Enteral nutritional supplementation in mechanically ventilated patients with organophosphorus poisoning - a randomised controlled trial

A dissertation submitted in partial fulfilment of the rules and regulation for the MD branch I (General Medicine) examinations of the Tamil Nadu Dr MGR Medical University to be held in March 2007

Enteral nutritional supplementation in mechanically ventilated patients with organophosphorus poisoning - a randomised controlled trial

Acknowledgements

I am thankful to

Dr George John, Professor and Head, Medical Intensive Care Unit, for his valuable guidance;

Dr Alka Ganesh, Professor and Head, Department of Medicine 3 for her help in selecting this topic and conducting the study;

Ms Mahendri N, Head of Dietary department for organizing the enteral formulations and for her guidance;

and Dr John V Peter, Medical Intensive Care Unit, and Ms Vishali, Department of Biostatistics for their help and advice.

INDEX

ABSTRACT

Aim:

To study the effect of early enteral nutritional supplementation in intubated patients with OP posioning admitted to the medical ICU of a tertiary care hospital.

Methods:

Design of study - Randomized controlled trial, not blinded.

Outcomes - The primary outcome was the frequency of hospital acquired infections. Secondary outcomes were mortality, duration on ventilator, length of stay and feeding related complications.

Results:

The difference in total calories recieved was statistically significant. The primary and secondary outcomes were assessed in 59 patients. There were no differences in the rate of hospital acquired infections between the two groups. Stratification of patients according to average daily caloric intake also failed to demonstrate any benefit for the higher calorie group. Duration of stay in ICU and in hospital, and duration on ventilator showed insignificant trends towards better results for those patients not enterally fed. Tracheostomy was associated with prolonged hospital stay in both groups. Mortality was not affected by enteral feeding. Feeding related complications were less common than in other

studies. Early enteral feeding was found to be safe in this population.

Conclusion:

In patients admitted with organophosphorus poisoning needing mechanical ventilation, early enteral nutritional supplementation is safe but is not associated with improvement in incidence of infectious complications or mortality. It may prolong the duration on ventilator and the length of stay.

INTRODUCTION

Patients with undernutrition are common in hospital populations. These individuals have impaired immunity, wound healing, muscle strength, and psychological drive, and cope poorly with medical and surgical interventions. Patients may be malnourished at the time of admission, or malnutrition may be acquired during hospitalization when oral intake is inadequate or physically impossible, and nutrient losses are excessive. Malnourished persons, on average, stay in hospital approximately five days longer than the normally nourished, incurring approximately 50% greater costs. (1-3) Hospitals should therefore aim to provide adequate nutrition to all patients.

Respiratory failure due to organophosphorus (OP) poisoning (usually with suicidal intent) is a common cause for admission to intensive care units in India. Patients with OP poisoning who develop the intermediate syndrome often require prolonged invasive ventilatory support. Nosocomial infections frequently add to the mortality, morbidity and cost of care.

Patients in the Medical ICU with low caloric intake have been shown to have a significant increase in the rate of bloodstream infections, (4) other hospital acquired infections (5) and biochemical markers for inflammation. (6) There have been no studies on nutrition in the subset of OP poisoned patients. This is

a setting where parenteral nutrition may be challenged by cost, and enteral nutrition by unpredictable gut motility and absorption due to the atropine used as an antidote.

AIM OF THE STUDY

To study the effect of early enteral nutrition in patients admitted with organophosphorus poisoning needing mechanical ventilation.

REVIEW OF LITERATURE

Prevalence of malnutrition

A large proportion of critically ill patients are underfed according to established targets. The average caloric intake in Medical ICU patients was found to be 56% of ACCP targets. (7)

The incidence of malnutrition in hospitalized and chronic care facility patients ranges from 30-50%, but often goes undiagnosed and untreated due to poor physician training and awareness in this area.(7) Malnutrition has been found to occur in 40% of free-living persons >60 years old, and in 30-50% of all hospitalized and chronic-care facility patients. Krishnan et al found that 60% of COPD patients with acute respiratory failure were malnourished, and that malnutrition was more frequent in those patients requiring mechanical ventilation (74%) than in those who did not (43%). (7) Thomas et al who examined the prevalence of undernutrition in 837 geriatric patients over 14 months in a subacute care facility found a high prevalence of malnutrition(one third of patients) based on BMI and serum albumin. This group also had a higher rate of depression, longer length of stay and higher rate of readmission to an acute care hospital. Mortality was not found to be related to BMI.(8)

The metabolic milieu in critically ill patients

Stress, as in sepsis, burns, major surgery , myocardial infarction, causes an

outpouring of counter-regulatory hormones, cytokines and lymphokines. This results in changes in substrate utilization and substance synthesis rates, as well as catabolism and hypermetabolism. (9) This abnormal metabolic milieu causes disordered utilization of exogenously administered nutrients.

a)Glucose metabolism

Stress causes major alterations in glucose metabolism, including elevated endogenous glucose production (hepatic gluconeogenesis), reduced glucose utilization and hyperglycaemia, and insulin resistance. (10) The administration of exogenous glucose and carbohydrates to injured or septic patients either does not or only minimally diminishes the rate of gluconeogenesis. Despite the reduced utilization of glucose, it is still important to administer carbohydrates, because some body tissues are unable to use other substrates readily. Furthermore, glucose and carbohydrate intakes stimulate the secretion of additional insulin, an anabolic hormone, that promotes protein synthesis (11) and has an antilipolytic affect (12, 13).

Excessive glucose loads (> 4 mg/kg per min), especially when administered to acutely stressed patients receiving a total caloric intake greater than resting energy expenditure, results in a thermogenic response, elevation of blood glucose concentrations and production of additional carbon dioxide. This additional carbon dioxide must be excreted via the lungs. This can produce

difficulties in weaning off mechanical ventilation. A recent survey of US teaching hospitals by Schloerb et al demonstrated that many were feeding their patients more than 4.5mg/kg per min glucose, thus increasing the possibility of glucose overload. (14)

b)Lipid metabolism

Various stresses, including injury, sepsis and congestive heart failure, cause alterations in lipid metabolism. (15) Lipolysis is accelerated by beta 2-adrenergic stimulation. (16, 17) glucagon, TNF-alpha, IL-1, interferon-alpha and interferon-gamma. (18) The increase in lipolysis results in an increased systemic supply of free fatty acids. (19) Glucose infusions further increase the lipolytic rate during abdominal surgery because they increase sympathetic nervous system activity. (16)

Concern has been expressed over the possible immunosuppressive effects of lipid emulsions. (20) A recent study in trauma patients (21) attributed an increased incidence of infections to lipid emulsion administration. This has led to recommendations to limit fat calories to 30% of total calories. (22)

c)Protein metabolism

One of the hallmarks of the metabolic response to injury is catabolism (negative

nitrogen balance). There is accelerated proteolysis of skeletal muscle, which provides some of the substrate for increased hepatic gluconeogenesis. (23) The increased protein breakdown is thought to be modulated by the endocrine stress hormones, such as cortisol and the cytokines TNF-1 alpha, IL-1, IL-6 and interferon-gamma. (24)

Exogenous protein administration: The aim of administering exogenous protein or amino acid is to attenuate the breakdown of endogenous proteins by providing an alternate source of amino acids for gluconeogenesis and protein synthesis. Unfortunately, in the stressed state exogenously administered amino acids and protein are not well utilized and nitrogen balance remains negative well into the convalescent stage. In the acutely stressed state proteolysis is relatively unresponsive to the usual feedback mechanisms, such as the administration of exogenous glucose, protein or amino acids. In the catabolic state an intake of 1.2-1.5 g/kg per day protein/amino acid is recommended and higher amounts may cause a rise in blood urea nitrogen.

Route of administration: Enteral versus parenteral.

Physiologic and biochemical basis:

There has been increased emphasis on using the enteral route for nutritional support due to the need to maintain gut integrity and so limit the translocation of bacteria from the gut. (25) Lack of enteral intake, such as occurs among

postoperative and critically ill patients receiving only parenteral nutrition, is associated with small intestinal villus atrophy, decreased villus cell count and reduced mucosal thickness, but not with changes in crypt cell count. (26). *Intestinal permeability*, measured using the urinary lactulose : mannitol ratio, is increased. (26) Also, crypt length is increased and mucosal surface patterns change from finger-like to leaf-like microvilli. (27) These changes were reversed with enteral feeding. (26, 28) Similar changes, along with activation of the lamina propria mononuclear cells and enterocytes, were seen during nutritional depletion. (29, 30, 31)

These anatomic changes in and of themselves do not lead to bacterial translocation; further insult is needed. One such insult is *ischaemia-reperfusion injury* to the small intestines after resuscitation from an episode of shock, which may also itself change gut integrity. (32) In the stressed patient, the constantly proliferating gut tissues (epithelial and lymphoid cells) may have an inadequate supply of nutrients, further compromising gut integrity. (33)

These changes in gut integrity have led many to consider whether *intestinal translocation of bacteria* occurs in critically ill humans after a systemic insult. This concern is based on studies of animal models that describe the translocation of gut organisms across intestinal mucosa with enhanced permeability. This bacterial translocation leads to local activation of the gut's

immune inflammatory system (Peyer's patches and hepatic Kuppfer cells). The released cytokines and other mediators then exacerbate the already existing systemic inflammatory response syndrome leading to multiple organ failure. (34) There is inadequate evidence of translocation in humans. (35) Indirect evidence comes from patients with intra-abdominal sepsis who showed reduced numbers of immunoglobulin A and M plasma cells. It was speculated that the reduced expression of these immunoglobulins might favour bacterial adhesion to enterocytes. (36)

Post-trauma:

Enteral feeding compared to parenteral nutrition was found to produce greater increase in constitutive proteins and greater decrease in acute phase proteins after severe trauma primarily caused by reduced septic morbidity compared to parenteral nutrition. (6) Post injury total enteral nutrition (TEN) attenuates reprioritization of hepatic protein synthesis in patients sustaining major trauma, compared to total parenteral nutrition (TPN). (37) Patients with abdominal trauma on TEN (via needle catheter jejunostomy) had better restoration of traditional nutrition markers (albumin, transferrin, retinol binding protein), had lower rate of infections and lower septic morbidity. (38)

Kudsk (39) randomised 98 pts with blunt or penetrating trauma to receive either enteral or parenteral feeding for 15 days. There were significantly fewer

infectious complications in patients who received enteral feeding with particular benefit shown in the most severely injured patients. The author recommends enteral feeding as a primary therapy affecting the outcome of critically ill patients.

Acute pancreatitis:

Windsor et al (40) measured the acute phase response (CRP) and change in disease severity score (APACHE II) before and after starting EN in patients with acute pancreatitis, compared with PN. These parameters were significantly improved in the EN group, with no significant change in the PN group.

Kalfarentzos (41) noted fewer total complications ($p<0.05$) and lower risk of septic complications ($p<0.01$) in patients with acute severe pancreatitis receiving EN compared to those receiving PN. Further, the cost of nutritional support was three times higher in patients who received parenteral nutrition. Dervenis (42) reviewed 5 studies on enteral nutrition in patients with acute pancreatitis, including the above two. Four agree that a significant reduction in total (including septic) complications were observed in the enteral feeding group.

Sepsis:

In patients with SIRS randomized within 4 to 6 days within onset of sepsis to

receive either parenteral or enteral nutrition of the same composition, there was no reduction in either the incidence of multiple organ failure syndrome (MOFS) or mortality attributable to the route of nutrition administration. The parenteral nutrition group tended to have better visceral protein support; the enteral nutrition group had more gut complications. (43)

Studies favouring PN:

Woodcock et al noted a significantly higher incidence of inadequate nutritional intake in patients fed enterally than in those fed parenterally. Complications related to the delivery system and other feed-related morbidity were significantly more frequent in the EN groups compared with the TPN groups. EN was associated with a higher overall mortality. He concludes that patients in whom there is reasonable doubt as to the adequacy of gastrointestinal function should be fed by the parenteral route. (44)

Meta analyses and reviews on EN and PN:

A meta-analysis by Potter in 1998 of oral/enteral nutritional support trials, in more than 2000 patients of all types, showed that the pooled odds ratio for death by the end of scheduled follow up showed a reduced case fatality in treatment compared with control groups of 0.66 (0.48–0.91; 2p,0.01). (45) An extensive semi formal review of the literature on malnutrition and nutrition

support in hospital by Green in 1999 also concluded that targeted nutritional support is of benefit in reducing hospital complications, duration of stay, mortality, and costs. (5)

Heyland et al systematically reviewed 13 studies (46) comparing EN with PN. There was no difference in mortality across groups receiving EN or PN, (RR 1.08, 95% CI, 0.70, 1.65; p=0.7) PN had a higher rate of infections. Safety, cost, and feasibility considerations favored the use of EN over PN. Since patients receiving combined EN and PN at onset of nutritional support fared badly, the authors recommend nutritional support commencing solely with enteral feeding without combined parenteral nutrition in critically ill mechanically ventilated patients.

A meta-analysis by Heyland using 26 studies (47) examined the relationship between TPN and standard care (usual oral diet plus intravenous dextrose), and complications and mortality rates in surgical and critically ill patients. TPN had no effect on mortality and only lowered complication rates in malnourished patients. Studies published before 1988 had significant treatment effect, whereas those published after 1989 did not. Complication rates, but not mortality, were lower among patients who did not receive lipids.

In a meta-analysis of thirty RCTs (ten medical, 11 surgical, and nine trauma) by

Peter et al. (48) comparing early enteral nutrition to early parenteral nutrition (within 96 hours from ICU/hospital admission or surgery), including all hospitalized patients, the average caloric intake among the enterally fed was 1840 (SD 772). (p= 0.03) Feeding started within 30.4 hours (SD 18.0). The authors observed increases in infective complications (7.9%, P = 0.001), catheter-related bloodstream infections (3.5%, P = 0.003) and noninfective complications (4.9%, P = 0.003) with the use of parenteral nutrition when compared with enteral nutrition. The abovementioned results translate to a reduction of one patient with an infective complication for every 13 patients and one patient with a noninfective complication for 20 patients treated with EN. A reduction in hospital length of stay of 1.2 days with the use of EN compared to PN was also reported. The difference was statistically significant (p=0.004) as this meta analysis included 2430 patients in 30 studies. There was a significant increase in diarrheal episodes (8.7%, p=.001) in enterally fed patients.

A meta analysis of 13 studies by Gramlich et al (49) showed a significant decrease in infectious complications (relative risk = 0.64, 95% confidence interval=0.47 to 0.87, P 0.004). There was no difference in the number of days on a ventilator or length of stay in the hospital between groups receiving EN or PN (Standardized Mean Difference [SMD]=0.07, 95% confidence interval 0.2 to 0.33, P=0.6)

A meta analysis of EN versus PN including 20 studies by Braunschweig et al (50) looked at two subgroups: EN or standard care (oral diet plus intravenous fluids) compared with PN. There was no demonstrable effect of EN on mortality (RR, 0.96; 95% CI, 0.55–1.65), but infection rates were lower with EN (RR, 0.66; 95% CI, 0.56–0.79).

Simpson et al evaluated studies that used the intention-to-treat principle to compare PN versus EN. (51) The use of parenteral nutrition was associated with an increase in infectious complications (odds ratio 1.47, 95% confidence intervals 0.90-2.38, P = 0.12). When all the trials were aggregated, parenteral nutrition was associated with a significant reduction in mortality (odds ratio 0.51, 95% confidence intervals 0.27–0.97, P = 0.04), The findings were reversed when trials of elective surgery patients were excluded.

A review of the literature by Lipman (52) revealed little absolute evidence that enteral nutrition is better than parenteral nutrition, with the exception of lower cost and possible reduced septic morbidity in acute trauma patients. (53,54)

Timing of Nutritional support

The 'gut hypothesis' of multiple organ failure has led to the recommendation that enteral nutrition be started as soon as possible after surgery or in

nonsurgical patients after admission to the intensive care unit to preserve splanchnic flow and prevent mucosal breakdown.(55)

Briassoulis G et al studied the incidence of protein and fat depletion and the frequency of protein energy malnutrition during stress states in children, and investigated the influence of early eneteral feeding on nutrition indices and acute phase proteins. He concluded that early enteral feeding improves nutrition indices and outcomes, and that only repleted energy, not anthropommetric or nutrition indices was independently associated with survival. (56) Patients suffering head injury and requiring mechanical ventilation who received enhanced enteral nutrition (started at a feeding rate that met estimated energy and nitrogen requirements) from day 1 had more rapid neurologic recovery with reduced incidence of major complications and post injury inflammatory responses (reduction in the ratio of CRP to Albumin concentration upto day 6 after injury). (57)

Rubinson et al (4) conducted a prospective cohort study on medical ICU patients, where participants were grouped into one of four quartiles based on%age of ACCP recommended daily caloric intake achieved. The overall mean daily caloric intake for all study participants was only 49.4% (SD 29.3) of American College of Chest Physicians(ACCP) guidelines. An overall nosocomial bloodstream infection rate of 22.4% was noted. Rubinson observed that

receiving >=25% of recommended calories was associated with a significantly lower risk of bloodstream infection (relative hazard, 0.27; 95% confidence interval, 0.11-0.68). There was no significant difference among the 3 quartiles that received >=25% recommended calories. Only nosocomial bloodstream infections were evaluated in this study.

Ibrahim (58) compared early and late enteral feeding in 150 patients using a protocol where the 'early feeders' had a target of 25 kcal/kg on day 1, while the 'late feeders' received only 20% of the target until day 5. Close inspection however shows that both groups received little nutrition with the percentage of target achieved in the early feeders of only 28% and even less at 7% in the late feeders (p=0.001). The early feeders had a higher incidence of VAP compared to late feeders. The early feeders had a longer ICU stay of 13.6 compared with 9.8 days (p=0.04), corresponding with a higher incidence of VAP, but they had a non-significant trend to lower hospital mortality (20.7% compared with 26.7% in the late feeders)

DiGiovine's review (59) of data from 4,389 mechanically ventilated medical patients showed that absolute ICU mortality rate was lower in the early-feeding(<48 hours) group than in the late-feeding group (18.6% vs 22.8%). Hospital mortality was 29.5% in the early-feeding group compared with 34.6% in the late-feeding group (p values not available) There were no between-group

differences in the rates of hospital acquired pneumonia or gastrointestinal bleeding, or in the length of ICU stay.

Martin et al (60) demonstrated in a multicentre cluster RCT with 499 patients, that use of an evidence based algorithm for early implementation of enteral nutrition in critically ill patients leads to significantly more days of enteral nutrition- 6.7 vs 5.4 per 10 pt days ($p = 0.042$). However his results show that there was no difference in overall (EN + PN) daily caloric intake between the two groups (973kcal/day in the control group , 1266 kcal /kg/day in the intervention group, $p = 0.25$). Where EN was not possible within 24 hours, PN was started and the feasibility for EN was reviewed every 12 hours. Enteral and parenteral calories/day are not provided in this report. In our study, although an algorithm was followed for inititation and escalation of nutritional support, PN was not used. The algorithm in Martin's study produced significant reductions in mortality (24 compared to 37%, $p=0.047$) and hospital stay (25.4 compared to 34.3 days, $p=0.006$).

A meta analysis on post operative patients by Moore (53) in 1992 compared early enteral feeding with parenteral and demonstrated a reduction in postoperative septic complications in those fed enterally.

Heyland's systematic review (46) included 8 RCTs comparing early and delayed

nutrient intake in critically ill patients. EN was started within 24-48 hours of resuscitation in the early feeding group in all studies. On aggregating these studies, early EN was associated with a trend towards reduction in mortality (RR, 0.52; 95% CI, 0.25, 1.08; p = .08) when compared with delayed nutrient intake. Three of these studies reported infectious complications. When these were aggregated, early EN was associated with a trend toward a reduction in infectious complications (RR, 0.66; 95% CI, 0.36, 1.22; p=0.19) when compared with delayed nutrient intake. The author advises early EN with strategies to optimise delivery and precautions to avoid aspiration and other complications.

Optimum caloric supplementation:

Krishnan (7) observed an average intake of 50.6% of the ACCP target of 25 kcal/kg/day among medical ICU patients. He notes that patients receiving 33-65% of ACCP target had a significantly greater likelihood of achieving spontaneous ventilation prior to ICU discharge. Interestingly the group that received > 66% of ACCP target was associated with a significantly lower likelihood of both hospital discharge alive and spontaneous ventilation prior to ICU discharge. He concludes that moderate caloric intake (ie, 33 to 65% of ACCP targets; approximately 9 to 18 kcal/kg per day) was associated with better outcomes than higher levels of caloric intake.

Rubinson et al (4), in their prospective cohort study in medical ICU observed that receiving >=25% of recommended calories compared with <25% was associated with significantly lower risk of bloodstream infection (relative hazard, 0.24; 95% confidence interval, 0.10-0.60). Average daily serum glucose, admission serum albumin, time to initiating nutritional support, and route of nutrition did not affect risk of bloodstream infection. The overall mean daily caloric intake for all study participants was 49.4% (SD 29.3) of American College of Chest Physicians guidelines.

Content of nutritional support

Energy and nitrogen requirements:

A patient's nutrient needs vary with nutritional state, and their illness. Both inadequate or excessive feeding can be harmful. The American College of Chest Physicians recommends 25 kcal/kg/day of energy supplementation. (61) Very undernourished patients should start at rates of < 10 kcal/kg/day to prevent refeeding syndrome. Some experts would always commence feed cautiously in severely ill patients. In healthy individuals, a protein intake of well under 0.15 g N/kg/day (1 g N=6.25 g protein) is adequate to maintain nitrogen balance but this changes dramatically in acute illness as catabolic patients have very high nitrogen losses. In the past, this led to the use of very high protein feeds in patients who were very ill or undernourished but recent opinion suggests that this is unwise.(62,63) Most authorities therefore recommend early feeding at

maximum levels of 0.2–0.3 g N/kg/day and some recommend even lower levels during early feeding.

Micronutrients:

Micronutrients are required for the prevention or correction of recognised deficiency states and maintenance of normal metabolism and antioxidant status. Standard enteral feeds are supplemented with vitamins and trace elements. Many patients however do not receive full ETF and may have pre-existing micronutrient deficits, poor absorption, and increased demands. It therefore seems reasonable to give additional balanced micronutrient supplements. (1)

Fluids and electrolytes:

Fluid needs can usually be met by giving 30–35 ml/kg body weight although allowance must be made for excessive losses from drains, fistulae, etc. Most feeds contain adequate electrolytes to meet the daily requirements of sodium, potassium, calcium, magnesium, and phosphate, although specific requirements vary.

Studies on enhanced content enteral feeding:

A meta-analysis of 11 randomized trials of both critically ill and gastrointestinal malignancy patients (65) examined the issue of immunonutrition (ie enteral nutrition supplemented with arginine, omega-3 fatty acids and purines). This

formulation is purported to improve immune function and showed significant reductions in the risk of developing infectious complications and in hospital stay. No effect on mortality was observed.

The *Canadian clinical practice guidelines* for nutrition support in mechanically ventilated, critically ill adult patients, based on extensive review of literature strongly recommend:

(a) that enteral nutrition be used in preference to parenteral nutrition,

(b) the use of a standard polymeric enteral formula,

(c) initiating feeds within 24 to 48 hours of admission to ICU,

(d) that patients be cared for in the semirecumbent position,

(e) that arginine containing enteral products not be used.

(f) strategies to optimize delivery of enteral nutrition should be considered.

(g) a glutamine enriched formula should be considered for patients with severe burns and trauma. (46)

Enteral nutrition

Route

Gastrointestinal access for up to 4–6 weeks is usually achieved using nasogastric or nasojejunal tubes, although placement of percutaneous gastrostomy or jejunostomy access should be considered sooner if feeding is very likely to be prolonged. Since the advent of endoscopic placement, percutaneous gut access

has become popular for longer term use.

Nasogastric (NG) tubes

Most enteral feed is given into the stomach to allow the use of hypertonic feeds, higher feeding rates, and bolus feeding. Fine bore 5–8 French gauge NG tubes are now used unless there is a need for stomach aspiration, or administration of high fibre feeds or drugs via the tube. (66) Large bore PVC tubes should be avoided as they irritate the nose and oesophagus and increase the risks of gastric reflux and aspiration They also need frequent replacement as they degrade on contact with gastric contents. Polyurethane and silicone tubes last for at least one month.(1)

Nasojejunal (NJ) tubes

Jejeunal feeding may be indicated if there are problems with gastric reflux or delayed gastric emptying. It should also be used in unconscious patients who have to be nursed supine.

Percutaneous gastrostomy tubes

If enteral feeding is likely to be needed for periods more than 4-6 weeks, a gastrostomy tube can be inserted directly into the stomach through the abdominal wall, using relatively simple endoscopic or radiological techniques.(67)

A meta analysis in 2003 of gastric versus post-pyloric feeding (68) was unable to demonstrate a clinical benefit from post-pyloric feeding versus gastric tube feeding in a mixed group of critically ill patients including medical, neurosurgical and trauma ICU patients. The incidence of pneumonia, ICU length of stay and mortality were similar between groups. Because of the delay in achieving post-pyloric intubation, gastric feeding was initiated significantly sooner than was post-pyloric feeding.

Feed administration

Enteral tube feeds can be administered by bolus, or by intermittent or continuous infusion.(64)

Bolus feeding entails administration of 200–400 ml of feed down a feeding tube over 15–60 minutes at regular intervals. The technique may cause bloating and diarrhoea and bolus delivery into the jejunum can cause a "dumping" type syndrome and should therefore be avoided. Bolus feeding can be performed using a 50 ml syringe, either with or without the plunger. If the latter is removed, the syringe can be hung up to allow gravity feeding.

Continuous infusion may help with diarrhoea or prevent “dumping” in some patients but it also results in higher intragastric pH levels than bolus feeding

which can promote bacterial growth. It is commonly used for very ill patients but it should be changed for intermittent infusion as soon as possible. Continuous feed should not be given overnight in patients who are at risk of aspiration. Intermittent infusion provides moderate rates of feed provision via either gravity or pump.

Breaks in feeding of six hours or more are used, depending on patients' needs (for example, overnight feeding). Post pyloric feeding necessitates continuous administration due to the loss of the stomach as a reservoir.

Choice of feeds

The choice of feed to be given via ETF is influenced by a patient's nutritional requirements, any abnormality of gastrointestinal absorption, motility, or diarrhoeal loss, and the presence of other system abnormality, such as renal or liver failure. Most commercial feeds contain 1.0 kcal/ml, with higher energy versions containing 1.5 kcal/ml.

The following feeds are generally used.

1. Polymeric feeds—These contain nitrogen as whole protein. The carbohydrate source is partially hydrolysed starch and the fat contains long chain triglycerides (LCTs). Their content of fibre is variable and although most authorities recommend that fibre should be included (69) the evidence that higher levels are of real benefit is not strong.

2. Predigested feeds—These feeds contain nitrogen as either short peptides or, in the case of elemental diets, as free amino acids. Carbohydrate provides much of the energy content with the content variable in both quantity and the proportion provided as light chain triclycerides (LCTs) and medium chain triglycerides (MCTs). The aim of predigested diets is to improve nutrient absorption in the presence of significant malabsorption. Their importance is probably greater in maldigestive (for example, pancreatic disease) rather than malabsorptive states. In patients with a short gut and no colon their high osmolality can cause excess movement of water into the gut and hence higher stomal losses. (70)

Complications of enteral tube feeding

1)Tube insertion related complications

Although nasal intubation may cause discomfort, traumatic complications are uncommon if using fine bore NG or NJ tubes.(66,71) Perforation of a pharyngeal or oesophageal pouch can occur and intracranial insertion of feeding tubes has been reported.(72, 73) Accidental bronchial insertion is relatively common in patients with reduced levels of consciousness or with impaired gag/swallowing reflexes. Endotracheal tubes in ventilated patients do not necessarily prevent bronchial insertion, and ETF into the lungs or pleural space can be fatal. (74) Approximately 25% of nasogastric tubes “fall out” or are

pulled out by patients soon after insertion and tubes, especially those that are fine bore, can be displaced by coughing or vomiting. There is however no evidence to support the use of weighted NG tubes in terms of either placement or maintenance of position.(75)

2)Post insertion complications

Nasopharyngeal discomfort, nasal erosions, abscsess formation, sinusitis, otitis media, oesophagitis and oesophageal ulceration from local abrasion and gastro-oesophageal reflux and tube block can occur. (76)

3)Reflux and inhalation problems

Gastro-oesophageal reflux is more common when patients are given NG feeds supine (77) due to gravitational back flow and impaired gastro-oesophageal sphincter function secondary to the tube across the cardia. It is very common in patients with impaired consciousness or poor gag reflexes, occurring in upto 30% of those with tracheostomies (78) and 12.5% of neurological patients.(79) Aspiration may occur with no obvious vomiting or coughing, and pneumonia can develop silently. To minimise risks of aspiration, patients should be fed propped up by 30°or more, and should be kept propped up for 30 minutes after feeding.(69)

There is an increased risk of aspiration if gastric residues accumulate, and

therefore if a four hour aspirate is >200 ml, the feeding regimen should be reviewed. Although continuous pump feeding reduces gastric pooling, it is often used overnight and may therefore be more risky than bolus or intermittent feeding.(80) Iso-osmotic feeds cause better gastric emptying than high osmotic feeds(81). Promotility drugs like metoclopramide or erythromycin may be helpful. Post pyloric feeding makes aspiration less likely, but does not eliminate the problem.

Gastrointestinal problems

Nausea occurs in 10–20% of patients (82, 83) and abdominal bloating and cramps from delayed gastric emptying are also common.(69) ETF related diarrhoea occurs in up to 30% of enterally fed patients on medical and surgical wards and more than 60% of patients on intensive care units.(84-87) It can create serious problems from nutrient, fluid, and electrolyte losses, and from infected pressure sores and general patient distress.(69) Parenteral nutrition may be required if elimination of all other causes of gastrointestinal upset and/or administration of simple symptomatic treatments fails to resolve the problem. Constipation, with or without overflow, also occurs with ETF.

Metabolic complications of ETF

Artificial feeding of patients may cause a variety of metabolic problems, including deficiencies or excess of fluid, electrolytes, vitamins, and trace

elements.(88-90)

1)Hyponatraemia may occur when enteral nutrition is given to sick patients. (91) It is usually due to a combination of excessive use of intravenous fluids, such as 5% dextrose, in combination with the adverse effects from malnourishment and severe illness on normal membrane pumping.

2)Hypernatraemia is usually due to excess water loss or transient diabetes insipidus in neurosurgical patients.(90)

3)Between 10% and 30% of tube fed patients are hyperglycaemic (89) and may need oral antidiabetic agents or insulin, before and during feeding.

4)Refeeding syndrome:

When commencing feeds in patients who have recently starved, there is the danger of inducing refeeding syndrome. (92, 93) This condition is poorly understood but occurs, in part, because the body adapts to undernutrition by downregulating membrane pumping in order to conserve energy. Refeeding problems can be avoided by feeding for the first few days at low levels while generously supplementing and closely monitoring potassium, magnesium, calcium, and phosphate. Instigation of feeds at levels of approximately 20 kcal/kg/day is often suggested. Thiamine and other B vitamins must be given intravenously before any feed is started. Commencing high levels of feeding shortly after major surgery or during sepsis or multiorgan failure can cause insulin resistance, liver dysfunction and metabolic problems similar to refeeding. (93)

Incidence of ETF related complications:

Pancorbo-Hidalgo et al (94) observed the following rate of complications in 64 patients in an internal medicine unit (mean age 76.2 years): tube dislodgement (48.5%); electrolytic alterations (45.5%); hyperglycaemia (34.5%); diarrhoea (32.8%); constipation (29.7%); vomiting (20.4%); tube clogging (12.5%); and lung aspiration (3.1%). In a multicentre study by Montejo et al (95) in 1999 involving 400 patients, 62.8% of the enterally fed patients had a gastrointestinal complication (GIC) including high gastric residuals, 39%; constipation, 15.7%; diarrhea, 14.7%; abdominal distention, 13.2%; vomiting, 12.2%; and regurgitation, 5.5%. Enteral nutrition withdrawal as a consequence of noncontrollable GICs occurred in 15.2% of patients.

Mentec observed upper digestive intolerance in 46% of 153 patients fed by nasogastric tube. This mode of feeding led to a higher frequency of pneumonia, longer ICU stay and higher ICU mortality. (96)

OP poisoning - pathophysiology, disease burden and feeding related considerations - justification for the study:

Attempts to commit suicide by oral ingestion of OP compounds are common in the Indian subcontinent. OP poisoning is primarily due to inactivation of

acetylcholinesterase (AChE), a neurotransmitter that breaks down acetylcholine (ACh). ACh accumulates throughout the nervous system, resulting in muscarinic and nicotinic receptor overstimulation.

In a study by Agarwal, (97) 67% of OP poisoned patients in India had suicidal intentions, 16.8% were caused by occupational exposures and 15.8% were poisoned accidentally. Worldwide mortality studies report mortality rates from 3-25%.

OP poisoning produces muscarinic effects (bradycardia, hypotension, bronchorrhea, sialorrhea, abdominal cramps with nausea/vomiting and fecal and urinary incontinence, visual disturbance), nocotinic effects (fasciculations, cramping, weakness, diaphragmatic failure) autonomic effects (hypertension, tachycardia, pupillary dilatation, pallor), and CNS effects (anxiety, restlessness, confusion, ataxia, seizures, coma, tremors). 3 types of paralysis differentiated by their time of onset may occur:

-type 1 - acute paralysis due to persistent depolarization at the neuromuscular junction.

-type 2 - intermediate syndrome develops 24-96 hours after resolution of acute symptoms and manifests commonly as paralysis and respiratory distress and may last 4-18 days.

-type 3 - OP induced delayed polyneuropathy (OPIDP) occurs 2-3 weeks after

exposure to large doses of certain OPs. Recovery can take upto 12 months.

Atropine which is used as an antidote, depending on the dose, can suppress gastric and intestinal peristalsis, and can precipitate cardiac arrhythmias in patients with hypoxia or metabolic imbalance.

OP poisoning with toxic manifestations requires monitoring in an ICU, and has a high incidence of respiratory failure requiring mechanical ventilation even with adequate atropinization. It constitutes a common problem in medical ICUs in developing countries, with many patients in intermediate syndrome requiring prolonged ventilatory support upto 3 weeks. The clinical course is often complicated by ventilator associated and other nosocomial infections and other complications.

While interventions with direct effects on the pathophysiology of the disease have been evaluated in controlled trials, aspects like nutrition and the route of feeding in these patients present difficulties due to:
1) complex, unpredictable interactions of the toxin and its antidote with the aerodigestive tract and
2) the potentially higher rate of aspiration soon after poison ingestion and during the early phase of care, (induced emesis and orogastric lavage, which are frequently done without airway protection in developing countries)

Some clinicians use general guidelines with regard to the nutrition of OP poisoned patients, while others, anticipating difficulties with enteral feeding, maintain ventilated patients on a nil-orally regimen for one to two weeks. However, parenteral nutrition is seldom started due to financial constraints and the need for stringent asepsis and metabolic monitoring. There is no published literature on nutritional supplementation in OP poisoned patients, the preferred route of feeding, and the acual incidence of feeding related complications.

Epidemiology of OP poisoning at our centre:(Table 1)

Table 1: Organophosphorus poisoning and mortality, 1999-2005

Year	Total patients	OP poisoning (%total admissions)	Mortality of OP (%)
1999	758	111(14.6)	15(13.5)
2000	787	118 (15.0)	17(14.4)
2001	790	112 (14.2)	19(17.0)
2002	759	99 (13.0)	14(14.1)
2003	735	102 (13.9)	15(14.7)
2004	697	101 (14.5)	14(13.9)
2005	702	82 (11.7)	12(14.6)

The total number of patients admitted to the Medical ICU of the Christian Medical College, Vellore per year is 700-800. OP poisoning accounts for about 14% of these admissions, about 105 per year. Table 1 gives the yearwise incidence and mortality for organophosphorus poisoned patients from 1999 to

2005. (98) During this period (and presently), P2AM (pralidoxime) has not been used for OP poisoning since trials were published questioning its efficacy. (99)

PATIENTS AND METHODS

Definitions

Ventilator associated pneumonia(VAP) was diagnosed by the following criteria(100):

-Appearance of a new or progressive pulmonary infiltrate

-Temperature >38 or <36 deg Celsius

-WBC count >10,000 or <4000 /ul

-Purulent tracheobronchial secretions

The presence of chest infiltrates plus two of the remaining 3 criteria mentioned above has a sensitivity of 69% and a specificity of 75% for the diagnosis of VAP. Quantitative endotracheal aspirate was used in patients who satisfied criteria for VAP, with >=10^5 colony forming units taken as significant. (100)

Catheter related blood stream infection (CRBSI)(101):

Bacteremia or fungemia in a patient who has an intravascular dievice and:

1. >=1 positive result of culture of blood samples obtained from the peripheral vein.
2. Clinical manifestations of infection (eg fever, chills, and/or hypotension) and no apparent source for blood stream infection (with the exception of the iv catheter).

Aspiration pneumonia:

Development of a radiologically evident infiltrate in patients who are at increased risk for oropharyngeal aspiration. (102)

Study design: Prospective randomised controlled; not blinded.

Setting: Medical intensive care unit of a tertiary care university teaching hospital

Study duration: 13 months

Sample size calculation:

As there was no previous studies done on nutritional supplementation in OP poisoned patients, the data from a study on caloric intake and nosocomial blood stream infections by Rubinson et al was used to calculate sample size. (4)

In this study a significant difference in the rate of nosocomial blood stream infections was found between the groups receiving <25% average daily recommended calories (based on the American College of Chest Physicians guidelines) and those receiving >=25%. At 10-15 days in MICU, 0.169 of the patients in the 25-50% target calories group developed a bloodstream infection, while 0.42 of the patients in the <25% target calories group developed a

bloodstream infection. Using these data in our study, a sample size of 46 in each group would hav1e 80% power to detect a siginficant difference in proportions assuming that the test will be done at the 5% significance level (two sided).

Inclusion criteria:

All OP poisoning patients admitted to the Medical ICU needing mechanical ventilation.

Exclusion criteria:

(1) Patients with refractory hypotension at the time of randomization were excluded. Gut alimentation in these patients would increase splanchnic blood flow requirements, compounding hemodynamic instability.

(2) Features of intestinal obstruction (tense distended abdomen) or ileus

Outcomes:

Primary: Rate of hospital acquired infections-

(1) ventilator associated pneumonia (VAP)

(2) catheter related blood stream infection (CRBSI)

(3) urinary tract infection (UTI).

Secondary:

(a) Mortality

(b) Duration on ventilator (number of days on mechanical ventilation including period on non-invasive pressure support), length of stay in ICU

and in hospital

(c) Relationship between caloric intake and infectious complications

(d) Feeding related complications.

Randomization:

Patients were alloted to either control or intervention group based on previously published random digits. (103) Serial random numbers with allocation were noted in a book which was available to MICU staff who added the patient's name and hospital number against each entry as patients were recruited.

Blinding:

Blinding was not possible in view of the nature of the study.

Standard care in ICU:

Mechanical ventilation was initiated for respiratory failure. Monitoring, investigations and treatment of both groups of patients followed the standard protocol in the medical ICU. The Medical ICU uses the following regimen of atropine:

Atropinization: 1mg/5-10min till fully atropinized.

Maintenance: Infusion at 1mg/hour, increasing by 1-2 mg/hour every 10 min to rate required to maintain heart rate >110/min (day 1), >100/min (day 2), >90/min (day 3). Keep pupils dilated but avoid heart rate >150/min.

-After day 3, taper atropine.

Tracheostomy was done if ventilation was required or expected to be required for more than 10 days after which ventilation was continued for as long as indicated.

Intervention:

Intubated patients with OP poisoning admitted to Medical ICU during the period of the study were randomized, following which the control group received no early enteral nutrition while the intervention group received nasogastric feeds based on a pre determined protocol starting within 48 hours of admission. Hypocaloric supplementation (providing less than the daily requirement of energy, protein and fat) was the aim rather than meeting the recommended daily caloric requirements. (4,7) Both groups received intravenous glucose according to fluid/electrolyte requirements. Both groups were treated similarly after tracheostomy, ie received nasogastric bolus feeds according to the standard protocol in the medical ICU.

Hence the duration of the intervention was from the time of intubation to the time of tracheostomy / transfer out of MICU / death. In the case of patients reintubated in the ward after being transferred out of MICU, the event was noted and included in the analysis, but the study-feeds protocol was not restarted.

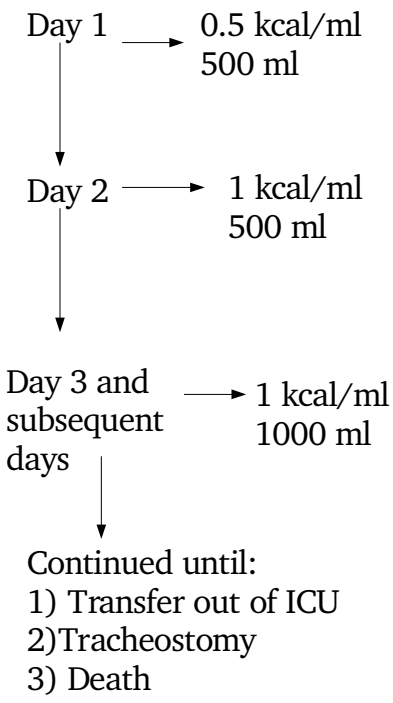
Enteral feeding:

Composition: according to standard nutritional guidelines. As all patients in the study were adults or adolescents, a target of 1000 Calories per day was the primary objective. Water was added to obtain a concentration of 1 Cal/ml. (The initial test feed was with 500 ml of 0.5 Cal/ml). (Table 1, Appendix B) Enteral feeds were prepared in the dietary department of the hospital.

Route and equipment:

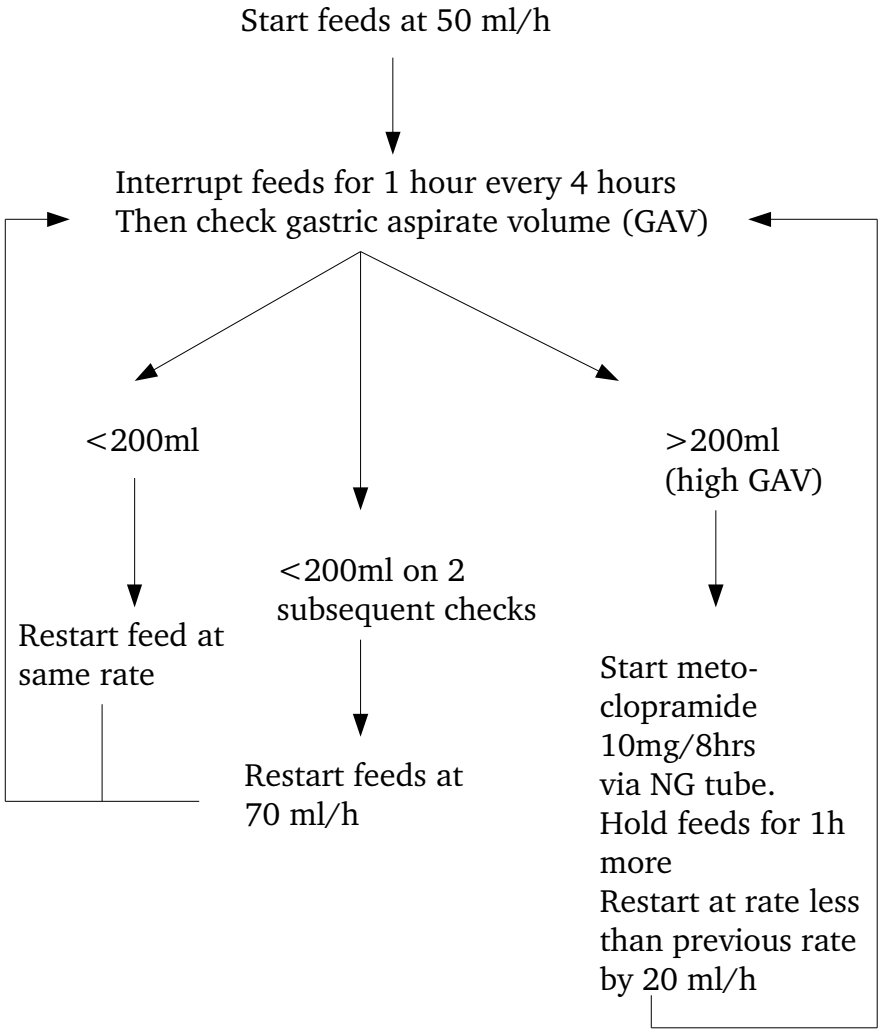
Patients in the intervention group received continuous enteral feeds delivered to

Fig 1: Schedule for enteral feeds



the stomach by a nasogastric tube. Tube position was confirmed by clinical methods. Enteral feeds were given according to the protocol given in Fig 1. Feed rate was adjusted and monitoring for gastric intolerance was followed according to the algorithm in Fig 2 (p 43). Goal rate of feeding was calculated

Fig 2 : Feed rate and gastric intolerance management



for 16-18 hours/day, taking into consideration interruptions in delivery. Feeds were escalated as per fig 1 depending on the patient's tolerance, ie, if there were two or more instances of gastric aspirate volume >200ml in a day, the same feed order was planned the next day.

Enteral feeds were continued till one of the following occured:

(1) transfer out of the ICU

(2) tracheostomy

(3) death.

Feeds were interrupted (104) :

-For 1 hour every 4 hours to check aspirate volume and tube position,

-For administration of drugs.

-Prior to tracheostomy, transfers for therapeutic/diagnostic procedures, and prior to extubation. Feeds were stopped 12 hours in advance, and if indicated, gastric contents were aspirated before the procedure.

Daily feed orders were written by the clinicians according to the protocol. The nursing staff were involved in administering the feeds according to the schedule, and followed the precautions and monitoring as per protocol. The head end of the bed was maintained at 30 degrees elevation unless contraindicated.

Monitoring:

Routine care included checking gastric residuals every 4-6 hr in patients receiving gastric feeding. Infusions were held for 1 additional hour if gastric residual was >200ml. Daily I/O records and serum electrolytes were monitored.

Evaluation

At the time of admission, patients were evaluated for aspiration, community acquired pneumonia, other infections and co-morbid conditions including chronic diseases. In the Medical ICU, nosocomial infections (ventilator associated pneumonia(VAP), catheter related blood stream infections(CRBSI) and urinary tract infection(UTI)), complications of enteral feeding and complications were documented. A treating consultant drew up appropriate treatment modifications. Following transfer to the general ward from ICU, patients were followed up for major events ie, re-intubation, discharge, death. Clinical examinations and ordering of relevant investigations and radiographs was done by the medical team as per standard protocol.

Data collection:

Data was collected on patients as they were recruited. Baseline characteristics and outcome variables were documented using a proforma that was updated daily till the time the patient left the ICU. A proforma was used for all patients (appendix C), and this data was transcribed onto a master sheet (appendix E).

Following transfer to the ward, the date of discharge or death was noted.

Statistical analysis

The analysis of the primary outcomes included data on all intubated patients with OP poisoning, according to an intention to treat. SPSS software was used. Analysis of adverse effects of enteral feeding was done on all patients who received any enteral feeds even for one day.

The Mann Whitney test (non parametric test of significance for 2 independent variables) for continuous variables and chi square test for nominal data were used to test for any significant difference in baseline characteristics- age, sex, serum pseudocholinesterase at admission, albumin on day 1 and the frequency of diabetes mellitus. Mann Whitney test was chosen as the data were not normally distributed. A two-tailed p value of 0.05 was taken to indicate statistical significance. Average daily caloric intake for each patient was computed, and the intervention (iv and enteral feeds) and control (calories by iv route only) groups were compared for a significant difference in mean caloric intake.

Primary and secondary outcome (frequency of nosocomial infections, duration on ventilator, incidence of reintubation and length of stay) were compared in the two groups using Mann Whitney test or Chi square test depending on the

type of variables. Patients who died were excluded from the analysis of duration on ventilator and length of stay in ICU and hospital.

The patients in the two groups were clubbed together and stratified according to daily calorie intake. Patients receiving <=500 kcal were compared with those receiving > 500kcal.

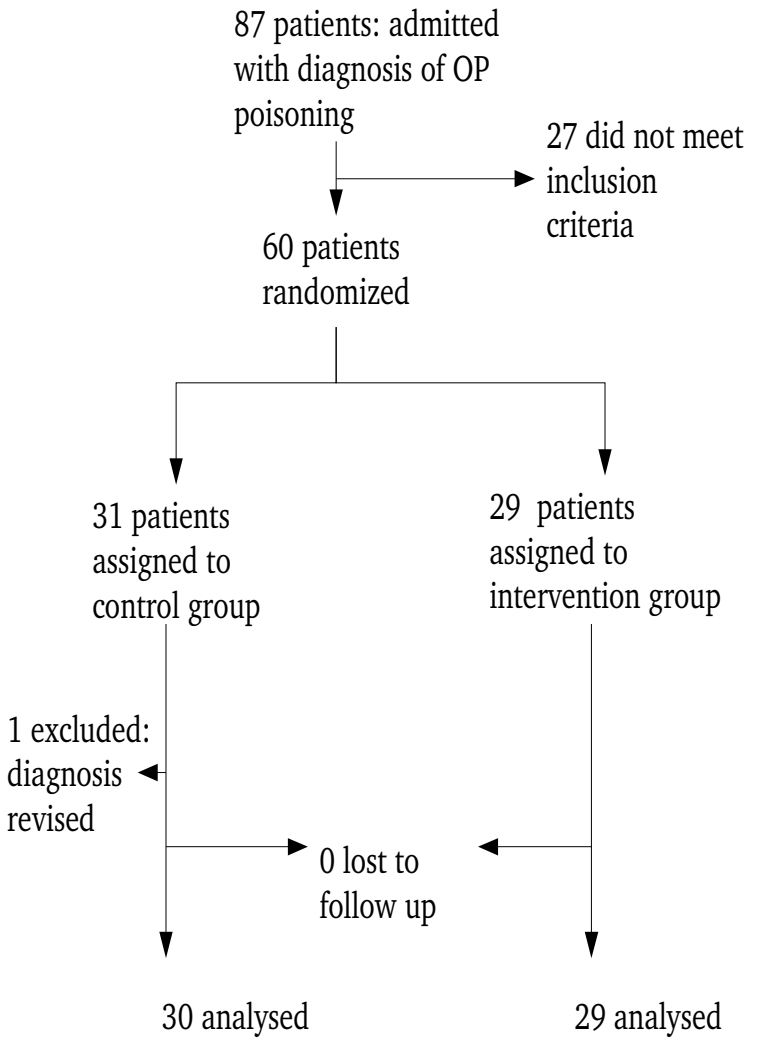
Subgroup analysis:

This was done post hoc for important groups to identify the influence of other factors on these outcomes, ie, albumin and VAP, use and timing of tracheostomy on VAP and on length of stay, and the time of VAP and nutrition.

RESULTS

Baseline characteristics:(Fig 3, Table 2)

Fig 3: Pathway for enrolment, randomization and follow-up



87 patients were admitted to Medical ICU from 1 January 2005 to 5 February 2006 with a diagnosis of OP poisoning. 60 patients who required intubation

Table 2 : Baseline characteristics					
			Intervention(SD)	Control(SD)	p value
Clinical	Age	Mean	29.41(11.8)	30.83(12.4)	0.86
		Median	26.000	27.500	(Mann Whitney test)
	Sex	Male	22	22	0.82
		Female	7	8	(Chi-square test)
Biochemical	No of diabetics	Number	2	3	0.56
					(Chi-square test)
	Pseudochol	Mean	562.59(539.4)	548.2(489.7)	0.79
		Median	428	412.74	(Mann Whitney test)
	Albumin-day 1	Mean	4.1(.668)	4.22(.866)	0.24
		Median	4.2	4.6	(Mann Whitney test)

fulfilled inclusion criteria and underwent randomization, 31 controls and 29 intervention. One patient randomized to the control group was excluded from analysis as the clinical features and pseudocholinesterase level were not suggestive of organophosphorus poisoning, and the diagnosis was revised as unknown poisoning. Hence the final analysis was done on 30 control and 29 intervention patients. As the study was completed in hospital there was no further attrition of the sample. The planned sample size of 46 in each group could not be attained during the study period.

The two groups were similar with respect to clinical (age, sex, presence of diabetes) and biochemical parameters (serum pseudocholinesterase and albumin on day 1).

Duration of follow up:

The mean duration of follow up in ICU for the intervention and control groups

was 10.28 (SD 5.47) and 8.93(SD 4.32) days respectively and the difference was found to be statistically insignificant. (p=0.41)

Patient demographic parameters:

Age: The patient population had a mean age of 30.14 years (SD 12.04), and the two groups were statistically similar with a mean age of 29.41 years (SD 11.8) in the intervention group and 30.83 years (SD 12.4) in the control group. (p=0.861)

Sex: There were 22 males and 7 females in the intervention group and 22 males and 8 female in the control group. (p=0.82)

Biochemical parameters:

Diabetes: There were 2 patients with diabetes mellitus type 2 in the intervention group and 3 in the control group. (p=0.56).

Serum Pseudocholinesterase level: Mean serum pseudocholinesterase at the time of admission was 555 U/L (SD 510.4), with no significant difference between the intervention (562.59 U/L, SD 539.4) and control (548.20, SD 489.7) groups (p=0.761).

Serum albumin level: Mean serum albumin on day 1 was 4.15 g/dl (SD 0.74). The intervention group had an albumin of 4.1 g/dl(SD 0.668) and the control group had an albumin of 4.22 g/dl (SD 0.866) with no significant difference between the two groups (p=0.243).

Analysis of outcome in intervention and control groups:(Table 3)

Table 3: Total calories, Nosocomial infections, Failed extubations, Tracheostomy				
	Both groups	**Intervention(SD)**	**Control(SD)**	**p value**
Calories total(iv+oral)				
Mean	559.14(SD 208.12)	671(243)	451(69.9)	p<0.0001(MannWhitney)
Mortality, n=6(10.16)	6(10.17%)	3(10.34%)	3(10%)	0.965(Chi-square test)
VAP	22 (37%)	12(41.38%)	10(33.33%)	0.523(Chi-square test)
CRBSI	7 (11.86%)	3(10.34%)	4(13.33%)	0.723(Chi-square test)
UTI	7 (11.86%)	2(6.89%)	5(16.67%)	0.246(Chi-square test)
Instances of infection	36	17	19	0.917(Chi-square test)
Pts who developed infections	29(49.15%)	14(48.28%)	15(50%)	0.898(Chi-square test)
Failed extubations	2(3.39%)	1(3.44%)	1(3.33%)	0.981(Chi-square test)
Timing of Tracheostomy				
No who had trach	23	14(48.27%)	9(30%)	0.24 (Chi square = 1.37)
Mean day of trach	7.260	6.360	8.670	0.007(Mann Whitney test)

C*aloric intake:* (Table 3)

The mean caloric intake per day in the entire group of patients was 559.14 kcal (SD 208.22). The control group received mean 451 kcal /day (SD 69.9). The intervention group received additional mean 262.6 kcal per day through nasogastric feeds and the average caloric intake in this group was 671 kcal (SD 243). The difference in caloric intake in the two groups was statistically significant (p<0.0001).

Primary outcomes:

Overall infection rate (Table 3):

There were 36 infectious compliations among 59 patients in both groups. 17 infectious complications occured among 29 patients in the intervention group and 19 among 30 patients in the control group. (p=0.917). Overall, 29 patients(49.15%) among the 59 had an infectious complication. 14 patients (48.28%) among the 29 in the intervention group and 15 patients (50%) among the 30 in the control group had an infectious complication. (p = 0.898)

Ventilator associated pneumonia: (Table 3)

The most common nosocomial infection in this population was VAP. 22 (37%) of 59 patients developed VAP of whom 12 were in the enterally fed group and 10 were in the group receiving standard iv fluids. The difference was not statistically significant. (p= 0.523)

Catheter related bloodstream infections (CRBSI) and urinary tract infection (UTI): (Table 3)

The incidence of catheter related bloodstream infection and UTI were both 7 of 59 patients (11.86%). The rate of these infections in the two groups was statistically similar (4 CRBSI and 5 UTI in the control group compared to 3 CRBSI and 2 UTI in the intervention group, p=0.723 for CRBSI and 0.246 for UTI, chi square test)

Secondary outcomes:

Mortality (Table 3):

3 patients did not survive in each group (p=0.965). In the control group 1 patient died of congestive heart failure, one of sepsis associated with VAP, and in one the cause of death was refractory hypotension. In the intervention group 2 patients died of sepsis associated with VAP and in one acute pancreatitis was the cause of death.

Tracheostomy (Table 3):

Tracheostomy was performed on 23 patients of whom 14 belonged to the intervention group and 9 belonged to the control group.(p = 0.24) Timing of tracheostomy (overall mean 7.26 days, SD 2.6) was found to be significantly earlier in the intervention group (mean 6.36 days, SD 2.53) compared to the control group (mean 8.67 days, SD 2.12) (p = 0.007).

Failed extubations: (Table 3)

1 patient in each group had to be reintubated following extubation. Both these patients had VAP, but survived and were successfully extubated subsequently.

Duration on ventilator: (Table 4)

The mean duration on ventilator in the patient population was 10.14 days.

Table 4: Duration on ventilator, Length of stay in ICU and in hospital				
		Intervention	**Control**	**p value**
Duration on ventilator	Mean	11.700	9.130	0.19
(n = 53)	Median	12.000	9.500	(Mann-Whitney test)
	Std deviation	6.431	4.974	
Days in ICU	Mean	10.280	8.930	0.41
(n =53)	Median	10.000	8.000	(Mann-Whitney test)
	Std deviation	5.470	4.323	
Days in Hospital	Mean	15.660	11.630	0.07
(n = 53)	Median	14.000	11.500	(Mann-Whitney test)
	Std deviation	8.545	5.762	

Patients enterally fed had an approximately 2 day greater delay in extubation compared to the control group, but the difference was not statistically significant. (p=0.186)

Length of stay: (Table 4)

In ICU: The mean stay in ICU was 9.59 days (SD 4.92). This was more than 1 day longer in the intervention group (10.28 days, SD 5.47) compared to the control group (8.93 days, SD 4.32). (p=0.411)

In hospital: The mean length of stay in hospital was 13.6 days (SD 7.48). Length of stay for the intervention group was 15.66 days (SD 8.55) and for the control group was 11.630 (SD 5.76). The difference of 4 days (p=0.067) was not statistically significant at the 95% confidence interval level.

Analysis of outcome based on total daily energy intake: (Table 5)

Patients were classified into two groups according to total caloric intake

Table 5: Comparison of outcome in patients with average daily intake <=500kcal (n=36) and >500kcal (n = 23)				
		<=500kcal(n=36)	>500kcal(n=23)	p value
VAP(n=22)		11(30.6%)	11(47.8%)	0.181
CRBSI(n=7)		4(11.1%)	3(13.0%)	0.823
UTI(n=7)		5(13.9%)	2(8.7%)	0.547
Days on Ventilator	Mean	9.060	10.610	0.067
(n = 53)	Std deviation	5.300	5.700	(Mann-Whitney test)
Days in ICU	Mean	8.970	10.130	0.382
(n = 53)	Std deviation	4.360	4.860	(Mann-Whitney test)
Days in Hospital	Mean	12.110	15.300	0.090
(n = 53)	Std deviation	6.440	7.930	(Mann-Whitney test)

irrespective of route of delivery. The group that received <=500kcal /day (36 patients) was compared to those who received > 500kcal /day (23 patients). (table 6) The incidence of VAP was 11/23 (47.8%) in the group that received > 500kcal energy/day compared to 11/36 (30.6%)in the group that received <=500kcal/day. The difference was not statistically significant (p= 0.181). CRBSI occured in 3 of 23 patients (13%) on >500kcal /day compared to 4 of 36 pts (11.1%) on <=500kcal/day. (p = 0.823) UTI occured in 2 of 23 patients (8.7%) on > 500 kcal/day and in 5 of 36 patients (13.9%) on <= 500 kcal/day. (p= 0.55)

The patients receiving >500kcal/day had a trend towards longer duration on ventilator (difference 1.55 days, p=0.067), longer stay in ICU (difference 1.16 days, p=0.382) and longer hospital stay (difference 3.11 days, p=0.09) but the differences were not statistically significant.

Feeding related complications:

2 patients (6.90% in the intervention group) had stasis, and one (3.44%) had aspiration syndrome, ie acute respiratory decompensation with/without radiographic findings with normal WBC count, no fever and no features suggestive of pulmonary embolism. There were no instances of nasogastric tube block or diarrhea in the intervention group.

Other complications:

As noted above one patient in the intervention group had pancreatitis, diagnosed on the 2nd hospital day. He received medical therapy, but failed to respond and expired on the 3rd hospital day. One 28 year old male patient in the control group who had VAP on multiple antibiotics had one episode of generalized tonic clonic seizures, treated with anticonvulsants, with no further adverse events. A 30 year old lady in the control group with rheumatic mitral valve disease developed cardiac failure on the second hospital day. She was treated unsucessfully with antifailure measures. Self-limiting acute non inflammatory diarrhea developed in one patient in the control group who also had VAP and UTI.

Post hoc analysis:

Based on the above findings some of the variables were analysed further for relevant associations.

Table 6: Time of VAP, Nutrition, Tracheostomy and Albumin level					
a) Time of diagnosis of VAP and nutrition					
	Early VAP	**Late VAP**	**p value**		
Mean total calories	540.300	718.360	0.023 (Mann Whitney test)		
Standard deviation	239.130	294.360			
b) Time of diagnosis of VAP in intervention and control groups					
	Feeds	**No feeds**	**p value**		
Mean VAP day	5.270	4.180	0.27 (Mann Whitney)		
SD	2.720	1.660			
c) Tracheostomy in patients with and without VAP					
Tracheostomy	**Total**	**Pts with VAP**	**Pts without VAP**	**p value**	
Trach	23	12	11	0.11 (chi square = 2.61)	
No trach	36	10	26		
Day of trach		6.420	8.180	0.190(Mann Whitney test)	
d) Albumin on day 1 (Albumin available for 26 patients)					
		VAP present	**VAP absent**		
No of patients		10	16		
Mean albumin		4.140	4.120		
Standard deviation		0.750	0.740		
		p = 0.43(Mann Whitney test)			

Serum Albumin and VAP: (Table 6d)

Serum albumin at admission was similar in patients with and without VAP (p = 0.43).

Tracheostomy and VAP: (table 6c)

Of the 23 patients who underwent tracheostomy, 12 were in patients with VAP and 11 were in patients without VAP (p=0.11). Tracheostomy was more common and earlier in patients with VAP (54.55%, 6.42 days) than those who did not develop VAP(29.72%, 8.18 days) but these results were not statistically significant (p = 0.11 for frequency of tracheostomy and 0.19 for timing of

tracheostomy).

Time of onset of VAP and nutrition: (table 6b)

VAP was diagnosed at a mean of 5.27 days on 12 patients in the intervention group which received enteral nutrition compared to 4.18 days on 10 patients in the control group who did not receive enteral nutrition. (p= 0.27)

An association between nutritional supplementation and time of onset of VAP was evaluated by classifying the patients with VAP into early VAP and late VAP, the cut off being 4 days as per the ATS definition. (105) Each category had 11 patients (n = 22). Patients who developed VAP early (<=4 days) were found to have a significantly lower caloric intake (540.3 kcal/day) compared to those who developed VAP later (>4 days) (718.36 kcal/day, p = 0.023). (Table 6a)

Tracheostomy and length of stay in hospital: (table 7)

Table 8: Tracheostomy and Duration of Hospital stay

	Trach	**No trach**	**p, Trach Vs No Trach**
Mean, both groups (n=53)	19.35	9.94	<0.0001
Std deviation, both gps	6.4	5.62	
Mean, intervention gp (n=26)	20.79	10.87	<0.0001
Std dev, intervention gp	7.02	7.03	
Mean, control gp (n=27)	17.11	9.29	<0.0001
Std dev, control gp	4.83	4.42	
p value(intervention vs	0.15	0.45	
control groups)			

Patients were classified according to presence or absence of tracheostomy. There was no difference in the length of hospital stay between the intervention and control patients in the group that had tracheostomy ($p = 0.15$) and the group that did not ($p = 0.45$). Patients who underwent tracheostomy had a significantly longer hospital stay than those who did not, irrespective of their route of caloric supplementation. ($p<0.0001$)

DISCUSSION

Extent of nutritional supplementation:

Hypocaloric nutritional supplementation has been found both in RCTs (58) and in prospective studies (7, 4) to have significant advantage over no nutritional supplementation, and to be better than full nutritional supplementation in non-surgical patients. The increased risk of prolonged ventilator requirement, duration in ICU (7,58) and greater mortality (7)associated with early full nutritional supplementation may be attributable to feeding related complications. This study was aimed at identifying benefits and problems associated with hypocaloric enteral nutritional supplementation. While both groups received standard iv fluids containing dextrose, the intervention group received nasogastric feeds less than ACCP guidelines.

Safety of enteral feeding:

This trial demonstrates that enteral feeding is safe in this patient population. The incidence of feeding related complications was much lower than described in other studies. (94-96) Risk factors for feeding related complications in these studies included age, high gastric aspirate volume prior to feeding and use of catecholamines during EN. Our patients had few of these risk factors; the mean age was 29 years and they had few comorbidities. The regimen of iv atropine used as an antidote did not interfere with enteral feeding.

Gastric stasis and Aspiration:

Continuous feeding was used instead of bolus feeding with the aim of improving gastric tolerance in the early stages of feeding. However, flow rates were unpredictable as infusion pumps were not used for delivering feeds. A feeding protocol was followed, and precautions to reduce the risk of aspiration were followed, ie, elevating the head end of the bed, checking gastric aspirate volume and tube position at intervals, use of prokinetic agents, stopping feeds prior to tracheostomy or extubation.

The occurrence of iatrogenic complications with the administration of enteral feedings is relatively common in the ICU. Mentec et al (94) observed that the presence of high gastric aspirate volumes was an early marker of upper digestive intolerance. This was associated with a higher incidence of nosocomial pneumonia, a longer ICU stay, and a higher ICU mortality.

Both silent and overt aspiration of gastric contents into the bronchial tree has been known to occur even in patients whose airway is protected by a cuffed endotracheal or tracheostomy tube. (106) This affects gas exchange in critically ill patients and can contribute to atelectasis and ventilator associated pneumonia, leading to delayed extubation, greater requirement for tracheostomy, prolonged ICU stay and increased mortality. Only two patients in the intervention group in our study had high gastric aspirate volume. Neither

had a nosocomial infections, and both survived.

The value of using gastric residual volume has been questioned by McClave et al (107) who demonstrated that aspiration syndrome occured even with no aspiratable gastric content. The mean residual volume(RV) for all aspiration events was 30.6 ml in this study. Raising the designated RV for cessation of enteral tube feeding from 200 mL to 400 mL did not increase the risk, because the frequency of aspiration was no different between controls (21.6%) and study patients (22.6%). Studies in which smaller feeds were used (4, 7) have shown reduction in bloodstream infections and duration on ventilator, although Rubinson (4) pointed out that the benefit did not depend on the route of supplementation.

Circulatory compromise:

High calorie enteral feeds in patients with borderline cardiorespiratory reserves, may impair microcirculation in vital organs by causing increased splanchnic circultion. Various authors (108, 109) demonstrate the need for extra caution and close monitoring during enteral feeding in these patients. However its safety in this setting has also been shown in a recent study. (110) We did not oberve any significant hemodynamic problems due to enteral feeds in our study.

Diarrhea:

None of the patients fed enterally had diarrhea. The low mean daily enteral caloric intake was probably the main reason for this. Further, the maximum feed concentration was 1 kcal/ml. Feeds were prepared under sterile conditions in the dietary department. A closed system of continuous enteral delivery was used to minimise microbial contamination. Most patients were on antibiotics either as prophylaxis or treatment for pneumonia, but there were no cases of antibiotic associated colitis. A high incidence of diarrhea, 14 to 32% was described in other trials (94, 95).

Effect of nutritional supplementation on outcome:

Nosocomial infection rate: (Table 4)

Bloodstream infections:

A previous prospective study (4) shows a significant reduction in the rate of blood stream infections, irrespective of the route of feeding as long as >=25% of daily requirements are supplied. A meta-analysis by Peter (48) show a significant drop in the rate of blood stream infections with enteral nutritional supplementation. The present study on mechanically ventilated OP poisoned patients has an insignificant reduction in blood stream infections and urinary tract infection and an insignificant overall decrease in hospital acquired infections with enteral feeding.

The mechanism by which providing small amounts of calories to critically ill patients could protect from development of nosocomial bloodstream infections remains speculative. Small volumes of enteral nutrition, by protecting against translocation of bacteria across the bowel wall may be partly responsible for some of the protection against infection. (34,35) In Rubinson's study, however, participants receiving parenteral nutrition are also seen to benefit. (4) The absence of additional benefit with increasing caloric intake also cannot be explained.

Ventilator associated pneumonia:

Ventilator associated pneumonia was more common in enterally fed patients but the difference was not statistically significant. Various authors (96, 95) caution against large volume enteral feeds in hospitalised patients as aspiration of gastric contents and development of VAP is a well documented complication. (107) A recent trial (58) conducted on a group of mechanically ventilated medical ICU patients was notable for the increased incidence of VAP associated with attempting to provide the full daily requirements soon after intubation. None of the studies and meta-analyses on enteral feeding show a reduction in the incidence of VAP. (4,7,48,49,58-60) In our study, feeds were started at low volumes and escalated with close monitoring.

The failure of nutritional supplementation to reduce VAP rates in our and other

studies could be due to various factors:

(a) Baseline nutritional status was normal, and prevalence of serious comorbidities was low in our patients. Thus, in the relatively short ICU stay, the absence of nutritional supplementation in the control group may not have sufficiently affected their immune and physiologic reserves.

(b) The difference in the mean number of daily calories received by the two groups, though highly significant statistically, was only 220 kcal. The control group received a mean of 451 kcal/day as dextrose in iv fluids. Significant reductions in bloodstream infections in medical ICU patients with as little as one fourth of ACCP daily nutritional targets (ie about 6 kcal/kg/day) have been described by Rubinson et al, (4) but this prospective study had not evaluated the effect of nutritional supplementation on VAP. Rubinson notes that this benefit was irrespective of the route of feeding, and that there was no difference among the groups that received 25-50%, 50-75% and 75-100% of ACCP guidelines. It is possible, therefore, that our patients in the control group had adequate nutrition (about 7.5 kcal/kg/day) to reduce not only the rate of bloodstream infections but also of VAP.

(c) Various studies and reviews have described iatrogenic complications associated with enteral feeding. The present study has a remarkably low rate of feeding related complications.

Duration on ventilator, length of stay in ICU and hospital: (Table 4)

The enterally fed group showed a trend towards longer ventilator dependance, longer ICU and hospital stay. These results were not statistically significant. Nevertheless, the potential clinical significance of a two day shorter period on ventilator, one day shorter ICU stay and four day shorter hospital stay for patients maintained on standard iv fluids cannot be overlooked and may indicate a trend.

Few studies and reviews on enteral nutritional supplementation report significant reductions in the days on ventilator (7), days in ICU (none) and days in hospital (48, 60). A meta-analysis by Gramlich et al (49) showed no difference between enterally and parenterally fed patients in duration on ventilator, and length of stay in ICU and hospital, similar to our findings. A population of mechanically ventilated Medical ICU patients who received early enteral feeding had a significant prolongation in ICU and hospital stay compared to those who received minimal calories enterally. (58)

Thus it is evident that no definite conclusions can be reached on the effect of enteral nutrition on length of stay and ventilator dependence.

Failed extubations: (Table 3)

We observed a low rate of failed extubation in both groups, with no difference

between the two groups. A thorough assessment of suitability for weaning by the clinician may have reduced this risk. The study protocol required temporary cessation of feeds prior to extubation to reduce the risk of aspiration.

Caloric intake and outcomes: (Table 5)

Two studies (4, 7) show that modest levels of caloric intake produce reductions in the rate of bloodstream infections and ventilator dependence, irrespective of route of nutritional supplementation. In our study, the control group received calories intravenously, while the intervention group received calories both intravenously and enterally. We combined both groups and classified patients according to mean daily caloric intake irrespective of route of feeding.

Patients who received <= 500 kcal/day and those who received > 500 kcal/day had similar rates of nosocomial infections, and similar requirements for ventilator support and ICU and hospital care. The mean caloric intake per day was 559 kcals (SD = 208.22). Only two patients were in the <25% ACCP target quartile described by Rubinson (4). Our findings are similar to his with respect to the other three quartiles (25-50%, 50-75% and 75-100%) in that there was no further benefit with further increasing the daily calories.

We noticed that patients who developed early VAP (<=4days) had a significantly lower overall caloric intake compared to those who developed late

VAP (>4 days). (p = 0.023) (Table 6c) This seems to imply that a higher caloric intake delays the onset of VAP, irrespective of the route of delivery. This benefit, however did not improve related outcomes, ie, duration on ventilator and length of stay which actually showed an unfavourable trend as overall caloric intake increased. (Table 5)

Mortality: (Table 3)

The overall mortality of 6 among 59 patients (0.17%) in our study was similar to the existing rate for OP poisoned patients requiring mechanical ventilation at our center. Three of these deaths were associated with nosocomial infections, of whom 2 were in the intervention group. The other 3 deaths were due to unrelated causes.

Two studies (59,60) demonstrate a significant reduction and one (58) an insignificant reduction in mortality among ICU patients who received enteral nutrition. However two meta-analyses (48, 49) fail to demonstrate an advantage in survival associated with enteral feeding. Some of the studies report methodologic difficulties, eg in Ibrahim's RCT (58) goal rates of feeding were not reached in either group. The early feeders had a significantly higher incidence of VAP and a longer ICU and hospital stay, but they had a non-significant trend to lower hospital mortality (20.7% compared with 26.7% in the early feeders). All studies show that enteral feeding is safe, and this is

confirmed by our study. Our failure to demonstrate a significant mortality benefit may be attributable to our small sample size, the overall good prognosis of OP poisoning and the fact that even the control group received some calories intravenously.

Tracheostomy: (Table 3)

Tracheostomy was performed earlier (6.36 versus 8.67 days, $p = 0.007$) and on more patients (14 versus 9, $p = 0.24$) in the intervention group than in the control group. We searched for associations between tracheostomy and VAP as there was an insignificantly higher rate of VAP in the intervention group. However, there was no significant difference in the rate and timing of tracheostomy between those who had VAP and those who did not.

As tracheostomy was more common in the intervention group which also had a non-significant trend towards longer hospital stay, the association of tracheostomy with enteral feeding and length of hospital stay was evaluated. (Table 7) Among patients who had a tracheostomy, the intervention and control patients had a similar length of hospital stay. The same finding was seen among those who did not need a tracheostomy. However tracheostomy was associated with a longer hospital stay irrespective of the presence ($p < 0.0001$) or absence ($p < 0.0001$) of enteral feeding.

Patients with more severe illness, prolonged intermediate syndrome or VAP may need ventilation for a longer period, hence it follows that they are more likely to have both a tracheostomy and a longer hospital stay. Frutos-Vivar (64) studied the use of tracheostomy in a much larger heterogenous population of 5081 mechanically ventilated patients. A longer ICU stay (21 versus 7 days, $p < 0.001$) and hospital stay (36 versus 15 days, $p < 0.001$) with similar hospital mortality (39 versus 40%, $p = 0.65$) were observed among those who had a tracheostomy compared to those who did not have a tracheostomy, as in our study. However, the incidence of tracheostomy (10.7%), timing (median of 12 days, interquartile range 7-17) and mortality (about 40%) were different from findings in our homogenous population of OP poisoning patients (incidence 38.9%, mean timing 7.26 days, SD 2.6, mortality 10.16%).

Unfortunately tracheostomy was not randomised within groups, and was decided on by the treating clinicians as per the current ICU protocol.

Limitations

While some limitations were noted at the time of planning, others were recognized during data collection and analysis.

Inadequate number of patients:

The study was designed to recruit 92 patients with 46 in each arm. However the

incidence of OP poisoning was lower during the study period than earlier. (table 1) At the planned end of the data collection phase, only 59 patients could be studied. This affected the distribution of data which did not approximate normality, hence the less sensitive non-parametric test had to be used to assess statistical significance.

The value of subgroup analysis was affected by the small size of the sample. The differences in outcome between the intervention and control group were small, hence this study with 30 patients in each arm was inadequately powered, eg, a power of only 10% to detect a significant difference in proportions of VAP in the two groups at the 5% significance level.

It must be noted that most other studies done on homogenous populations had similar or smaller numbers. Peter's meta-analysis (48) included 30 studies (2430 patients), each with about 40 patients in each arm. Gramlich's meta-analysis (49) included 13 studies, most with <30 patients in each arm.(Table 2, Appendix B)

Blinding:

Blinding was not possible given the planned intervention. As many clinicians and nurses would have been aware of which group a particular patient belonged to, there was potential for bias.

Inadequate feeding:

It had been planned to supplement less than the daily requirement of calories, but planned feeding goals could not be reached in many patients. ACCP guidelines recommend a daily target of 25 kcal /kg/min. This translates to about 1500 kcal/day in the average built adult. Based on literature we had planned for a feeding goal of 1,000 kcal/day. There were various reasons for the failure to reach goal rates of enteral feeding.

(1)Delay in starting/escalating feeds: There were frequent delays in ordering feeds among clinicians and in informing the dietary department among nurses for logistic reasons.

(2)Interpretation of complications: While the protocol defined stasis as >200ml gastric aspirate after a 1 hour interval following 4 hours of feeding, the nursing staff were sometimes reluctant to advance feeding plans with smaller aspirate volumes, and especially with findings such as greenish aspirate. There were many instances when caregivers witheld or delayed progression in feed plans due to suspected stasis or risk of aspiration. These instances were not picked up by the study definition in which a gastric aspirate volume of >= 200ml was classified as gastric intolerance.

(3)Interrupting feeds for procedures: When procedures such as tracheostomy

were planned, the patient would be kept fasting, but sometimes feeds would not be restarted if the planned procedure was postponed for logistic reasons. Patients would therefore remain with no enteral intake for 2-3 days following which some clinicians restarted (at the low inititation rate) rather than continued the feeding plan (at the higher maintenance rate).

Due to these factors the intervention group received 671 kcal/day (SD 243), instead of 1000kcal/day. However, as discussed above, other studies have shown benefit with similar caloric supplementation (4,7,58), and reviewers have published evidence based recommendations for hypocaloric supplementation (46)

CONCLUSIONS

1) Early enteral feeding is safe in mechanically ventilated patients admitted with OP poisoning. The incidence of feeding related complications was markedly lower than in other similar trials.

2) The regimen of atropine used in these patients does not seem to impair gastrointestinal motility to affect early enteral feeding.

3) Enteral feeding shows no significant effect on infectious complications - ventilator associated pneumonia, catheter related bloodstream infections or urinary tract infections.

4) Enteral nutrition had no significant effect on mortality.

5) Early enteral feeding may be associated with more days on ventilator, and longer ICU and hospital stay.

Reference List

1. Stroud M, Duncan H, Nightingale J. Guidelines for eneral feeding in adult hospital patients. Gut 2003;52 Suppl 7:1-12.

2. Robinson G, Goldstein M, Levine GM. Impact of nutritional status on length of stay. JPEN J Parenter Enteral Nutr 1987;11:49–51.

3. Reilly JJ Jr, Hull SF, Albert N, Waller A, Bringardener S et al. The economic impact of malnutrition: A model system for hospitalised patients. JPEN J Parenter Enteral Nutr 1988;12:371–6.

4. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA: Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 2004;32:350-357.

5. Green CJ. Existence, causes and consequences of disease related malnutrition in the hospital and the community, and the clinical and financial benefits of nutritional intervention. Clin Nutr 1999;18 Suppl 2:3–38.

6. Kudsk KA, Minard G, Wojtysiak SL, Croce M, Fabian T, Brown RO. Visceral protein response to enteral versus parenteral nutrition and sepsis in patients with trauma. Surgery 1994 Sep;116(3):516-23.

7. Krishnan JA, Parce PB, Martinez A, Diette GB, Browner RG. Caloric intake in medical ICU patients- consistency of care with guidelines and relationship to cinical outcomes. Chest 2003;124:297-305.

8. Thomas DR, Zdrowski CD, Wilson MM, Conright KC, Lewis C, Tariq S et al.

Malnutrition in subacute care. Am J Clin Nutr 2002 Feb;75(2)308-13.

9. Weissman C. Nutrition in the intensive care unit. Crit Care 1999;3:R67–R75.

10. Strommer L, Permert J, Arnelo U, Koehler C, Isaksson B, Larsson J et al. Skeletal muscle insulin resistance after trauma: insulin signaling and glucose transport. Am J Physiol 1998;275:E351-E358.

11. Wolfe, RR: Substrate utilization/insulin resistance in sepsis/trauma. Ballieres Clin Endocrinol Metab 1997;11:645-57.

12. Fellander G, Nordenstrom J, Ungerstedt U, Arner P, Bolinder J. Influence of operation on glucose metabolism and lipolysis in human adipose tissue: a microdialysis study. Eur J Surg 1994;160:87-95.

13. Jeevanandam M, Shamos RF, Petersen SR. Substrate efficacy in early nutrition support of the critically ill multiple trauma victims. J Parenter Enteral Nutr 1992;16:511-20.

14. Schloerb PR, Henning JF. Patterns and problems of adult total parenteral nutrition use in US academic medical centers. Arch Surg 1998;133:712.

15. Kupari LJ, Yki-Javinen H. Free fatty acid kinetics and oxidation in congestive heart failure. Am J Cardiol 1998;81:45-50.

16. Fellander G, Nordenstrom J, Tjader I, Bolinder J, Arner P. Lipolysis during abdominal surgery. J Clin Endocrinol Metab 1994;78:150-5.

17. Herndon DN, Nguyen TT, Wolfe RR, Maggi SP, Biolo G, Muller M et al. Lipolysis in burned patients is stimulated by the beta-2-receptor for catecholamines. Arch Surg 1994;129:1301-5.

18. Doerrler W, Feingold KR, Grunfeld C. Cytokines induce catabolic effects in cultured adipocytes by multiple mechanisms. Cytokine 1994;6:478-84.

19. Breitenstein E, Chiolero RL, Jequier E, Dayer P, Krupp S, Schutz Y. Effects of beta-blockade on energy metabolism following burns. Burns 1990;16:259-64.

20. Waitzberg DL, Bellinati-Pires R, Salgado MM, Hypolito IP, Colleto GM, Yagi O et al. Effect of total parenteral nutrition with different lipid emulsions on human monocyte and neutrophil functions. Nutrition 1997;13:128-32.

21. Battistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. J Trauma 1997;43:52-60.

22. Chan S, McCowen KC, Blackburn GL. Nutritional management in the ICU. Chest 1999;115 Suppl:145S-148S.

23. Tashiro T, Yamamori H, Takagi K, Morishima Y, Nakajima N. Effect of severity of stress on whole-body protein kinetics in surgical patients receiving parenteral nutrition. Nutrition 1996;12:763-5

24. Brown JA, Gore DC, Jahoor F. Catabolic hormones alone fail to reproduce the stress-induced efflux of amino acids. Arch Surg 1994;129:819-24.

25. Archer SB. Current uses and abuses of total parenteral nutrition. Adv Surg 1996;26:165-189.

26. Buchman AL, Moukarzel AA, Bhuta S, Belle M, Ament ME, Eckhert CD et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J Parenter Enteral Nutr 1995;19:453-60.

27. Sedman PC, MacFie J, Palmer MD, Mitchell CJ, Sagar PM. Preoperative total parenteral nutrition is not associated with mucosal atrophy or bacterial translocation in humans. Br J Surg 1995;82:1663-7.

28. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med 1995;152:1545-8.

29. Van der Hulst RR, von Meyenfeldt MF, van Kreel BK, Thunnissen FB, Brummer RJ, Arends JW et al. Gut permeability, intestinal morphology, and nutritional depletion. Nutrition 1998;14:16.

30. Welsh FK, Farmery SM, MacLennan K, Sheridan MB, Barclay GR, Guillou PJ et al. Gut barrier function in malnourished patients. Gut 1998;42:396-401.

31. Reynolds JV, O'Farrelly C, Feighery C, Murchan P, Leonard N, Fulton G et al. Impaired gut barrier function in malnourished patients. Br J Surg 1996;83:1288-91.

32. Kong SE, Blennerhassett LR, Heel KA, McCauley RD, Hall JC. Ischaemia-reperfusion injury in the intestine. Aust NZ J Surg 1998;68:554-61.

33. McBurney MI. The gut: central organ in nutrient requirements and metabolism. Can J Physiol Pharmacol 1994;72:260-5.

34. Swank GM, Deitch EA. Role of the gut in multiple organ failure: bacterial translocation and permeability changes. World J Surg 1996;20:411-7.

35. Lipman TO. Bacterial translocation and enteral nutrition in humans: an outsider looks in. J Parenter Enteral Nutr 1995;19:156-65.

36. Coutinho HB, Robalinho TI, Coutinho VB, Amorim AM, Furtado AF, Ferraz A et al. Intra-abdominal sepsis: an immunocytochemical study of the small intestine mucosa. J Clin Pathol 1997;50:294-8.

37. Peterson VM, Moore EE, Jones TN, Rundus C, Emmett M, Moore FA et al. Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic protein reprioritization. Surgery 1988 Aug;104(2):199-207.

38. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM: TEN versus TPN following major abdominal trauma--reduced septic morbidity. J Trauma. 1989 Jul;29(7):916-22.

39. Kudsk KA: Gut mucosal nutritional support-enteral nutrition as primary therapy after multiple system trauma. Gut 1994 Jan;35(1 Suppl):S52-4.

40. Windsor AC, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI et al: Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998 Mar;42(3):431-5.

41. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA: Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. Br J Surg 1997 Dec;84(12):1665-9.

42. Dervenis C. Enteral nutrition in severe acute pancreatitis: future development. J Pancreas 2004;5(2):60-63.

43. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM: Enteral nutrition does not prevent multiple organ failure (MOFS) after sepsis. Surgery 1988 Oct;104(4):727-33.

44. Woodcock NP, Zeigler D, Palmer MD, Buckley P, Mitchell CJ, MacFie J. Enteral versus parenteral nutrition: a pragmatic study. Nutrition. 2001 Jan;17(1):1-12.

45. Potter J, Langhorne P, Roberts M. Routine protein energy supplementation in adults: a systematic review. BMJ 1998;317:495-501.

46. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian Critical Care Clinical Practice Guidelines Committee: Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003 Sep-Oct;27(5):355-73.

47. Heyland DK, MacDonald S, Keele L, Drover JW. Total parenteral nutrition in the critically ill patient. JAMA 1998, 280:2013-19.

48. Peter JV, Moran JL, Phillips-Hughes J: A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med. 2005 Jan;33(1):213-20

49. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004;20:843-8.

50. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: A meta-analysis. Am J Clin Nutr 2001;74:534-42.

51. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med 2005;31:12-23.

52. Lipman TO. Grains or veins: is enteral nutrition realy better than parenteral nutrition? A look at the evidence. J Parenter Enteral Nutr 1998;22:167-82.

53. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. The results of a meta-analysis. Ann Surg 1992;216:172-83.

54. Hall JC, Heel K, McCauley R. Glutamine. Br J Surg 1996;83:305-12.

55. Frost P, Bihari D. The route of nutritional support in the critically ill: physiological and economic considerations. Nutrition 1997;13 (suppl):58S-63S.

56. Briassoulis G, Zavras N, Hatzis T. Malnutrition, nutritional indices, and early enteral feeding in critically ill children. Nutrition 2001 Jul-Aug;17(7 Suppl 8):548-57.

57. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial

to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 1999 Nov;27(11):2525-31.

58. Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, Fraser V et al. Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. J Parenter Enteral Nutr 2002;26:174-81.

59. Gale Jurasek. Is early enteral feeding a good idea? [Online]. 2004[cited 2006 Jul 31]; Available from: URL:http://www.pulmonaryreviews.com/feb04/pr_feb04_enteralfeeding.html

60. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ 2004 Jan 20;170(2):197-204.

61. Cerra FB, Benitez MR, Blackburn GL, Irwin RS, Jeejeebhoy K, Katz DP. Applied nutrition in ICU patients: a consensus statement of the American college of chest physicians. Chest 1997;111:769-78.

62. Jeejeebhoy KN. Bulk or bounce - the object of nutritional support. JPEN J Parenter Enteral Nutr 1988;12:539–46.

63. Elia M. Changing concepts of nutrient requirements in disease: implications for artificial nutrition support. Lancet 1995;345:1279–84.

64. Frutos-Vivar F, Esteban A, Apezteguia C, Anzueto A, Nightingale P, Gonzalez M et al. International Mechanical Ventilation Study Group: Outcome of mechanically

ventilated patients who require a tracheostomy. Crit Care Med. 2005 Feb;33(2):290 -8.

65. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. Ann Surg 1999;229:467-77.

66. Rees RG, Attrill H, Quinn D, Silk DB. Improved design of nasogastric feeding tubes. Clin Nutr 1986;5:203–7.

67. Moran BJ, Taylor MB, Johnson CD. Percutaneous endoscopic gastrostomy. Br J Surg 1990;77:858–62.

68. Marik PE, Zaloga GP: Gastric versus post-pyloric feeding: a systematic review. Critical Care 2003;7:R46-R51

69. Duncan HD, Silk DB. Problems of treatment - enteral nutrition. In: Nightingale J, editor. Intestinal failure. London: Greenwich Medical Media Ltd; 2001. p. 477–96.

70. McIntyre PB, Fitchew M, Lennard Jones JE. Patients with a jejunostomy do not need a special diet. Gastroenterology 1986;91:25-33.

71. Silk DB, Rees RG, Keohane PP, Attrill H et al. Clinical efficacy and design changes of “fine bore” nasogastric feeding tubes: a seven-year experience involving 809 intubations in 403 patients. JPEN J Parenter Enteral Nutr 1987;11:378–83.

72. Iyer V, Reichel J. Perforation of the oesophagus by a fine bore feeding tube. N Y State J Med 1984;84:63–4.

73. Wyler AR, Reynolds AF. An intracranial complication of nasogastric intubation. J Neurosurg 1977;47:297–8.

74. Mensforth A, Nightingale J. Insertion and care of enteral feeding tubes. In: Nightingale J, editor. Intestinal failure. London: Greenwich Medical Media Ltd, 2001. p. 281–303.

75. Keohane PP, Attrill H, Silk DBA. Clinical effectiveness of weighted and unweighted 'fine bore' nasogastric feeding tubes in enteral nutrition: a controlled clinical trial. J Clin Nutr Gastroenterol 1986;1:189–93.

76. Marcuard SP, Stegall KL, Trogdon S. Clearing obstructed feeding tubes. JPEN J Parenter Enteral Nutr 1989;13:81–3.

77. Sriram K, Jayanthi V, Lakshmi RG, George VS. Prophylactic locking of enteral feeding tubes with pancreatic enzymes. JPEN J Parenter Enteral Nutr 1997;21:353–5.

78. Nagler R, Spiro SM. Persistent gastro-oesophageal reflux induced during prolonged gastric intubation. N Engl J Med 1963;269:495–500.

79. Winterbauer RH, Duming RB, Barron E, McFadden MC. Aspirated nasogastric feeding solution detected by glucose strips. Ann Intern Med 1981;95:67–8.

80. Olivares L, Segovia A, Revuelta R. Tube feeding and lethal aspiration in neurological patients: a review of 720 autopsy cases. Stroke 1974;5:654–7.

81. Jacobs S, Chang RWS, Lee B, Bartlett FW. Continuous enteral feeding: A major cause of pneumonia among ventilated intensive care unit patients. JPEN J Parenter

Enteral Nutr 1990;14:353–6

82. Bury KD, Jambunathan G. Effects of elemental diets on gastric emptying and gastric secretion in man. Am J Surg 1974;127:59–66.

83. Jones BJM, Lees R, Andrews J, Frost P, Silk DB. Comparison of an elemental and polymeric enteral diet in patients with normal gastrointestinal function. Gut 1983;24:78–84.

84. Keohane PP, Attrill H, Love M, Frost P, Silk DB. Relation between osmolality of diet and gastrointestinal side effects in enteral nutrition. BMJ 1984;288:678–80.

85. Rees RG, Keohane PP, Grimble GK, Frost PG, Attrill H, Silk DB. Elemental diet administered nasogastrically without starter regimens to patients with inflammatory bowel disease. JPEN J Parenter Enteral Nutr 1986;10:58–62.

86. Kelly TWJ, Patrick MR, Hillman KM. Study of diarrhoea in critically ill patients. Crit Care Med 1983;11:7–9.

87. Benya R, Layden TJ, Morbarhan S. Diarrhoea associated with tube feeding: the importance of using objective criteria. J Clin Gastroenterol 1991;13:167–72.88. Ho CS, Yee AC, McPherson R. Complications of surgical and percutaneous non-endoscopic gastrostomy: Review of 233 patients. Gastroenterology 1988;95:1206–10.

88. Gallagher MW, Tyson KRT, Ashcraft KW. Gastrostomy in pediatric patients: an analysis of complications and techniques. Surgery 1973;74:536–9.

89. Woolfson AM, Saour J, Ricketts CR, Pollard BJ, Hardy SM, Allison SP. Prolonged

nasogastric tube feeding in critically ill and surgical patients. Post Grad Med J 1976;52:678-82.

90. Gault MH, Dixon ME, Doyle M, Cohen WM et al. Hypernatraemia, azotemia and dehydration due to high protein tube feeding. Ann Intern Med 1968;68:778–91.

91. Solomon S, Kirby DF. The refeeding syndrome: a review. JPEN J Parenter Enteral Nutr 1990;14:90–7.

92. Havala T, Shronts E. Managing the complications associated with refeeding. Nutr Clin Pract 1990;5:23–9.

93. Flatt JP, Blackburn GL. The metabolic fuel regulatory system: implications for protein-sparing therapies during caloric deprivation and disease. Am J Clin Nutr 1974;27:175–87.

94. Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Ramirez-Perez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. J Clin Nurs. 2001 Jul;10(4):482-90

95. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units.Crit Care Med. 1999 Aug;27(8):1447-53.

96. Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med. 2001 Oct;29(10):1955-61.

97. Agarwal SB. A clinical, biochemical, neurobehavioral, and sociopsychological study of 190 patients admitted to hospital as a result of acute organophosphorous poisoning. Environ Res 1993 Jul;62(1):63-70

98. Sudarsanam TD, Pichamuthu K, Zachariah A, John G. Oximes in acute organophosphate poisoning [Letters to the editor]. Critical Care Medicine 2006;34(8):2265.

99. Cherian AM, Peter JV, Samuel J, Jaydevan R, Peter S, Joel S et al. Effectiveness of P2AM (PAM -Pralidoxime) in the treatment of organophosphorus poisoning (OPP): a randomized, double blind placebo controlled clinical trial. J Assoc Physicians India 1997; 45:22-24.

100. Rajasekhar T, Anuradha K, Suhasini T, Lakshmi V. The role of quantitative cultures of non-bronchoscopic samples in ventilator associated pneumonia. Indian J Med Microbiol 2006;24:107-113

101. Mermel LA, Barry MF, Sheretz RJ, Raad II, O'Grady N, Harris JS et al. Guidelines for the managtement of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249–72

102. Marik PE. Aspiration pneumonitis and aspiration pneumonia. NEJM 2001;344:665-71.

103. Daniel WW. Biostatistics: a foundation for analysis in the health sciences, 7th ed. New York: John Wiley & Sons. Appendix A.

104. Fish J. Tube feeding in the ICU: overcoming the obstacles. [Online] [2005?]. [cited 2006 Jul 28]; Available from: URL:http://www.rosslearningcenter.com/default.asp?pageID=25&itemID=665

105. Niederman MS, Craven DE. Hospital acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy and preventive strategies. A consensus statement, American Thoracic Soceity, November 1995. Am J Respir Crit Care Med 1996;153(5):1711–25

106. Metheny NA, Clouse RE, Chang YH, Stewart BJ, Oliver DA, Kopllef MH. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors.Crit Care Med. 2006 Apr;34(4):1007-15.

107. McClave, Lukan JK, Stefater JA, Lowern CC, Looney SW, Matheson PJ et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. Crit Care Med. 2005 Feb;33(2):324-30.

108. McClave SA, Chang WK. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? Nutr Clin Pract. 2003 Aug;18(4):279-84.

109. Melis M, Fichera A, Ferguson MK. Bowel necrosis associated with early jejunal tube feeding: A complication of postoperative enteral nutrition. Arch Surg. 2006 Jul;141(7):701-4.

110. Revelly JP, Tappy L, Berger MM, Gersbach P, Cayeux C, Chiolero R. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. Intensive Care Med. 2001 Mar;27(3):540-7.

Appendix A

Abbreviations

ACCP	American college of chest physicians
ACh	Acetylcholine
AChE	Acetylcholine Esterase
CRBSI	Catheter related blood stream infection
EN	Enteral nutrition
ETF	Enteral tube feeding
GAV	Gastric aspirate volume
GIC	Gastrointestinal complications
JCAHO	Joint council on accreditation of health care organizations
LCT	Long chain triglycerides
MCT	Medium chain triglycerides
MICU	Medical ICU
NG	Nasogastric
NJ	Nasojejunal
NSAID	Non steroid anti inflammatory drug
OP	Organophosphorus
PN	Parenteral nutrition
PPI	Proton pump inhibitor
PEGJ	Percutaneous endoscopic transgastric jejunostomy
RCT	Randomised controlled trial
RV	Residual volume
SCFA	Short chain fatty acids
SD	Standard deviation
TEN	Total enteral nutrition
TPN	Total parenteral nutrition
VAP	Ventilator associated pneumonia
UTI	Urinary tract infection

Appendix B : Tables

Table 1: Composition of MICU study feeds

Day	Fruit juice-gm (kcal)	Sugar gm (kcal)	Oil gm (kcal)	Rice flour gm (kcal) (gm protein)	Proteinex gm (kcal) (gm protein)	Tot vol ml	Tot energy kcal	Tot protein gm
Day 1	325 (130)	15 (60)	0	0	20 (60) (6.4)	500	250	6.4
Day 2	0	28 (112)	15 135)	35 (102) (2.24)	50 (150) (16.5)	500	500	18
Day 3	0	36 (144)	12.5 (125)	40 (136) (2.66)	35 (105) (11.5)	500 x 2 = 1000	500 x 2 = 1000	14.16 x 2 = 28.32
Day 4	0	92.5 (370)	45 (405)	125 (425) (8.2)	100 (300) (33)	1500	1500	41.5

Note: Feed quantity is advanced in the above schedule according to the patients tolerance. If, for example, the patient has gastric aspirate volume > 200 ml with Day 1 feeds, then Day 1 feeds are repeated on subsequent days till criteria are fulfilled for Day 2 feeds.

Table 2: RANDOMIZED CLINICAL TRIALS THAT COMPARED EN WITH PN IN CRITICALLY ILL PATIENTS - Gramlich L. (205)

Refs	Subjects		Population	Infection		Mortality		LOS		VD	
	EN	PN		EN	PN	EN	PN	EN	PN	EN	PN
29	23	23	Trauma and laparo	15 (65)	17 (74)	1 (4)	3 (13)	30	31	12	10
22	28	21	Head injury	N/A	N/A	5 (18)	1 (5)	39	37	N/A	N/A
23	31	35	Post sepsis	N/A	N/A	7 (22)	8 (23)	N/A	N/A	N/A	N/A
28	12	15	Blunt trauma	N/A	N/A	1 (7)	1 (8)	N/A	N/A	N/A	N/A
11	13	11	Cardiac bypass	N/A	N/A	2 (15)	6 (55)	N/A	N/A	N/A	N/A
24	21	24	Head trauma	17 (80)	15 (63)	3 (14)	2 (8)	N/A	N/A	N/A	N/A
32	18	20	Acute pancreatitis	5 (28)	10 (50)	1 (6)	2 (10)	11	12	15	11
16	51	45	Abdominal trauma	9 (16)	18 (40)	1	1	20.5	19.6	2.8	3.2
26	29	30	Abdominal trauma	5 (17)	11 (37)	0	0	N/A	N/A	N/A	N/A
25	118	112	High-risk surgical	19 (16)	39 (35)	8 (7)	11 (10)	17	22	N/A	N/A
30	18	20	Head injury	N/A	N/A	9 (50)	3 (15)	49.4	52.6	10.3	10.4
27	17	21	Malnutrition	6 (38)	11 (52)	9 (53)	5 (24)	33.2	27.3	N/A	N/A
31	28	23	Brain injury	5 (18)	4 (17)	10 (36)	10 (43)	N/A	N/A	N/A	N/A

EN, enteral nutrition; N/A, not available; PN, parenteral nutrition; VD, days on ventilator. References in column 1 have not been reproduced. Numbers in parentheses are percentages.

No of patients in EN arm	**No of studies**(205)
10-20	5
21-30	5
31-40	1
41-50	0
51-60	1
61-110	0
111-120	1

Appendix C1

1) Main Proforma

Name _____ Age _____ Pseudochol _____

Hosp No _____ Sex _____ Diabetes _____

Randomization: Intervention / Control

Date of admission to: Hospital._____ ICU _____

Date of discharge from: ICU _____ Hospital _____

No of Days: Ventilator _____ICU _____Hospital _____

Died : Y / N

Failed extubation: Y / N Tracheostomy: Y / N Trach days : _____

Albumin: On admission : _____ Day 7: _____ Drop in Albumin: _____

Calories/day Total : _____ NG: _____ IV: _____

Feeding relateed complications		Nosocomial infections		Day of onset
Stasis	: Y / N	Bloodstream infections	: Y / N	_____
Diarrhea	: Y / N	VAP	: Y / N	_____
Tube Block	: Y / N	UTI	: Y / N	_____
Aspiration	: Y / N	Others	: _____	

Other complications		Cause of death	
DVT	: Y / N	Sepsis	: Y / N
Pulm embolism:	Y / N	Hypoxic isch encephalopathy	: Y / N
Renal failure	: Y / N	Others	: _____
Others	: Y / N		

Appendix C2

2) Proforma for daily calories:

Hospital No: _____ Name: _____ Intervention / control

Day	iv calories	NG calories	Ventilator related events	Other events, Xray, etc
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				

Appendix D: Glossary of Master sheet headers

sno	Serial number
hno	Hospital number
init	Patients initials/ first and last letters of name
age	Age in years
sx	Sex, male=1, female=2
psch	Pseudocholinesterase level at admission, U/L
dm	Diabetes, present=1, absent=2
fed	Intervention=1, Control=2
doa	Date of admission
vntd	No of days on ventilator
icud	No of days in ICU
hosd	No of days in hospital
die	Expired=1, Survived=2
failx	Failed extubation=1, No failed extubation=2
trch	Tracheostomy done=1, No tracheostomy done=2
trchd	Day on ventilator when tracheostomy was done. 0=Tracheostomy not done
albd1	Albumin level at admission. ND=S.Albumin not done at admission
aldrp	Drop in albumin after 7 days. NA=Data not available.
calst	Average calories/day (NG+iv)
calsn	Average calories/day given NG
calsi	Average calories/day given iv
crbsi	Catheter related bloodstream infection, Yes=1, No=2
vap	Ventilator associated pneumonia, Occured=1, Did not occur=2
vapd	Day on ventilator when VAP was diagnosed. 0=VAP did not occur
uti	Urinary tract infection, occured=1, did not occur=2
oth	Other complications, pancreatitis=1, drug induced seizures=2, diarrhea=6, 0= not applicable
dtcs	Cause of death: cardiac failure=1, sepsis=2, pancreatitis=3, hypotension=9, 0= not applicable
stas	Gastric hypomotility in NG fed patients, Occured=1, Did not occur=2, 0= not applicable
diar	Diarrhea in NG fed patients, Occured=1, Did not occur=2, 0= not applicable
blck	NG tube block in NG fed patients, Occured=1, Did not occur=2, 0= not applicable
asp	Aspiration syndrome in NG fed patients, Occured=1, Did not occur=2, 0= not applicable